



Federatie
**Medisch
Specialisten**

COVID-19

Deze richtlijn is tot stand gekomen op initiatief van COVID-19

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Startpagina - COVID-19

Waar gaan de modules binnen deze richtlijn over?

In deze COVID-19 richtlijn staan adviezen over de zorg voor patiënten die (verdenking hebben op) COVID-19 of een infectie hebben doorgemaakt. De richtlijn is onderverdeeld in de volgende overkoepelende onderwerpen:

- Infectiepreventie
- Diagnostiek
- Behandeling
- Langdurige klachten en revalidatie na COVID-19

Voor wie zijn deze richtlijnmodules bedoeld?

Deze modules zijn bedoeld voor alle zorgprofessionals betrokken bij de zorg van patiënten en het met (verdenking op) COVID-19.

Voor patiënten

Voor patiënten is op Thuisarts.nl informatie te vinden over COVID-19 (<https://www.thuisarts.nl/corona>).

Hoe zijn de richtlijnmodules tot stand gekomen?

Na de uitbraak van SARS-COV-2 zijn er binnen het programma COVID-19 een groot aantal leidraden en handreikingen ontwikkeld en gepubliceerd op de website van de Federatie Medisch Specialisten. Deze leidraden en handreikingen zijn doorontwikkeld tot richtlijnmodules.

Infectiepreventie bij COVID-19

Waar gaat deze richtlijnmodule over?

De module niet meer besmettelijk na COVID-19 beschrijft aanbevelingen wanneer een COVID-19 bevestigde patiënt als niet meer besmettelijk kan worden beschouwd en isolatiemaatregelen kunnen worden opgeheven. Deze richtlijn COVID-19 geeft adviezen over de diagnostiek, behandeling en nazorg van patiënten met (verdenking op) COVID-19. Ook is er aandacht voor infectiepreventie. Deze richtlijn probeert zo de kwaliteit van de zorg aan patiënten met COVID-19 te verbeteren.

Voor wie is deze richtlijnmodule bedoeld?

Deze module is bedoeld voor alle zorgprofessionals betrokken bij de zorg van patiënten en het met (verdenking op) COVID-19 en diegene die verantwoordelijk zijn voor het opstellen van het infectiepreventiebeleid binnen de organisatie.

Informatie voor patiënten

Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over COVID-19. Daarnaast is voor patiënten met aanhoudende klachten na COVID-19 ook aanvullende informatie beschikbaar op het [Coronaplein](https://coronaplein.nl).

Hoe zijn de richtlijnmodules tot stand gekomen?

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Status van de richtlijn

Gedurende de pandemie zijn diverse leidraden gepubliceerd. Voor onderwerpen die momenteel (nog) niet als modules zijn gepubliceerd, verwijzen we u naar de website:

<https://www.demedischspecialist.nl/onderwerp/details/richtlijnen-handreikingen-leidraden>.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Niet meer besmettelijk na COVID-19

Uitgangsvraag

Wanneer is een COVID-19 patiënt niet meer besmettelijk en kunnen isolatiemaatregelen worden opgeheven?

Aanbeveling

Om een positieve COVID-19 patiënt niet meer als besmettelijk te beschouwen (COVID-19 vrij) wordt geadviseerd de volgende termijnen in acht te nemen:

Patiënt is:

- Immuuncompetent: Minstens 5 dagen na eerste ziektedag EN tenminste 24 uur klachtenvrij.
- Immuungecompromiteerd: Minstens 5 dagen na eerste ziektedag EN tenminste 24 uur klachtenvrij. Overweeg PCR van nasopharynx/keel. Bij lage Ct waarde (bijvoorbeeld < Ct24) overwegen de isolatie voort te zetten.

COVID-19 patiënt nog beademd en/of met tracheostoma:

- Op basis van het volgen van Ct waarden in meerdere diepe luchtwegmonsters zoals sputum of uitzuigsel, kan men na 14 dagen met aanhoudende hoge Ct waarden (bijvoorbeeld > Ct30) besluiten de isolatie te beëindigen.

Overwegingen

Virusweek wordt nu nog als de beste proxy gezien voor de aanwezigheid van besmettelijk virus en daarmee kans op transmissie. De kans op transmissie wordt vermoedelijk wel groter door de aanwezigheid van bepaalde klachten zoals hoesten, niezen of een loopneus. Daarnaast is niet zeker of met het aantonen van cytopathisch effect ook de minimale infectieuze dosis wordt bereikt om transmissie te bewerkstelligen. De studies gebruikt voor deze richtlijn bevestigen alle de aanwezigheid van infectieus virus met behulp van virusweek (Bullard 2020, To 2020, Wölfel, 2020, Huang 2020, van Kampen 2021, La Scola 2020, Walsh 2020, Basile 2021, Gniazdowski 2021, Sohn 2020, Folgueira 2020, Singanayagam 2020, Manzulli 2021, Li 2020, Aydillo 2020, Benotmane 2021, Laferl 2021, Owusu 2021, Sonleitner 2021, Yamada 2021, Glans 2021, Folgueira 2021, Ke 2021, Murrata 2021, Nomura 2021, Boucau 2021, Siedner 2021, Salvatore 2021, Glenet 2021, Fall 2022, Yonker 2021, Wu 2023).

Factoren die uitscheiding van kweekbaar virus beïnvloeden

In de overweging naar de aanbevelingen hieronder zijn meegenomen de invloed van: immuunstatus, ernst van de COVID-19 infectie, vaccinatiestatus, het hebben van (rest)klachten, virusvarianten, hoogte van de viral load, serologische respons en moment na de eerste ziektedag.

Immuunstatus en ernst van de ziekte

Bij immuun competente personen wordt bij het merendeel na 8-10 dagen geen kweekbaar virus meer gevonden (Bullard 2020, Wölfel 2020, Van Kampen 2021, Owusu 2021). In de studie van Yonker 2021 onder kinderen, nam de kans op het aantonen van kweekbaar virus al af na dag 5.

Bij ernstige ziekte kan kweekbaar virus mogelijk langer worden aangetoond, tot 10-14 dagen (Basile 2021, Walsh 2020, Nolimura 2021, Folguiera 2021, Young 2021).

Niet alle studies zijn hierin eenduidig; de resultaten van Mollan 2021 laten juist zien dat bij matige tot ernstige infectie infectieus virus eerder verdwijnt dan bij milde infectie, een effect dat in de multivariate analyse teniet wordt gedaan. Bij immuungecompromitteerden kan SARS-CoV-2 ook langer kweekbaar zijn. Globaal kan 14-21 dagen worden aangehouden, maar de spreiding is groot (Walsh 2020, Aydillo 2020, Benotmane 2021).

Vaccinatiestatus

Bij de delta variant werd in de studie van Salvatore 2021 geen verschil gezien in de duur van uitscheiding van kweekbaar virus tussen gevaccineerden en ongevaccineerden. In de studie van Ke 2021 was dit wel het geval, betreffende de alpha en gamma variant, in het voordeel van de gevaccineerden. In Fall 2022 tonen gevaccineerden minder uitscheiding van kweekbaar virus voor de delta variant, echter niet voor de omicron variant. De review van Wu includeerde zes studies die de duur van virus uitscheiding onderzochten in omicron positieve patiënten met verschillende vaccinatiestatus. Hoewel er geringe verschillen werden waargenomen bleken deze niet significant. Om deze reden wordt de vaccinatiestatus niet meegewogen in de genoemde adviezen. Er wordt geen onderscheid gemaakt tussen gevaccineerde en niet gevaccineerde patiënten.

(Rest)klachten

Symptomatische en asymptomatische personen vertonen vaak een vergelijkbare virale dynamiek (Singanayagam 2020, Yonker 2021). De vraag blijft in hoeverre de klachten zelf (hoesten, niezen, loopneus) bijdragen aan het transmissie risico op dat moment.

De studie van Gniazdowski 2021 noemt dat het aantonen van kweekbaar virus >14 dagen na de eerste ziektedag vaker werd gezien bij mensen die nog klachten hadden op dat moment, maar de groep was klein en de studie was niet opgezet om dit te onderzoeken. De werkgroep heeft geen studies gevonden die expliciet keken naar de mogelijke besmettelijkheid bij mensen met (respiratoire) restklachten.

Bij een patiënt die nog wordt beademd of een tracheostoma heeft worden veelvuldig handelingen verricht waarbij aerosolen kunnen vrijkomen. Men kan om pragmatische redenen de isolatie verlengen tot 14 dagen en vervolgens varen op herhaaldelijke PCR uitslagen. De werkgroep heeft geen literatuur gevonden om dit te onderbouwen.

Virusvarianten

Enkele studies vergelijken de duur van virusuitscheiding en kweken van verschillende virus varianten. In de studie van Fall 2022 lijkt bij de omicron variant de kans op het vinden van kweekbaar virus lager dan bij de Delta variant, maar er bleek geen duidelijk verschil in duur van uitscheiding. In de studie van Puhach 2022 werd geen significant verschil gevonden tussen omicron en delta, met een semi-kwantitatieve kweekmethode. In de studie van Siedner 2022 werd de delta variant vergeleken met alpha, gamma, mu (en onbekende varianten) waarbij voor de deltavariant een langere duur van uitscheiding werd gevonden vergeleken met de andere varianten. De resultaten van deze studie kunnen echter vertekend zijn doordat de personen met delta lange tijd na vaccinatie zijn opgevolgd.

De invloed van de verschillende virusvarianten op de duur van de uitscheiding is onduidelijk en lijkt in de huidige fase minder relevant. In de adviezen wordt daarom geen onderscheid gemaakt.

Viral load, serologische respons en timing na eerste ziektedag

Meerdere studies rapporteren een correlatie tussen de Ct-waarde en de viruskweek, waarbij het kweken van virus globaal gezien niet meer mogelijk lijkt uit materiaal bij Ct-waarden >30 (o.a. Bullard 2020, Huang 2020, Van Kampen 2021, Wölfel 2020, La Scola 2020, Sonnleitner 2021, Mollan 2021, Singanayagam 2020, Young 2021).

Samen met de hoogte van de Ct-waarde is ook de timing na de eerste ziektedag een belangrijke factor (zie ook Immunestatus en ernst van de ziekte).

Gemiddeld worden er binnen 2 weken antistoffen geproduceerd tegen SARS-CoV-2 (Long, 2020) en wordt het virus geneutraliseerd.

Enkele studies laten zien dat het aantonen van IgG en/of neutraliserende antistoffen voorspellend kan zijn voor het klaren van infectieus virus (Van Kampen 2021, Mollan 2021). De toepasbaarheid van dit gegeven in de praktijk wordt bemoeilijkt door IgG verworven door vaccinatie.

Bij een immunocompetent persoon heeft het doen van PCR of serologie geen toegevoegde waarde na gestelde periode (7 of 14 dagen); de PCR kan lang positief blijven zonder dat het iets zegt over de besmettelijkheid en de serologie kan laag-positief of zelfs negatief blijven. Men kan in deze situatie varen op de timing na de eerste ziektedag. Mocht een patiënt laat in het ziektebeloop positief testen en zich dus in het staartje van de infectie bevinden bij diagnose, dan kunnen PCR en serologie wel bijdragen om dit te bevestigen en de isolatie te bekorten.

Bij immuungecompromiteerde personen kunnen PCR en serologie extra informatie bieden. Omdat er grote variaties in Ct-waarden per laboratorium kunnen bestaan, kan geen exact advies worden gegeven, maar een negatieve PCR of een Ct-waarde bijvoorbeeld >30 kan worden gebruikt om de isolatie op te heffen. Als extra hulpmiddel kan een IgG seroconversie worden gebruikt.

Waarden en voorkeuren van patiënten

Isolatie- en quarantaine maatregelen worden ingezet ter voorkoming van verspreiding van het virus. Patiënten in isolatie kunnen mogelijk o.a. psychosociale effecten, stress en angst ervaren. Het is daarom belangrijk om de besmette persoon en diens wettelijk vertegenwoordiger(s) mee te nemen in de beslissing en duidelijk te informeren waarom isolatie wordt toegepast en wat er van de patiënt verwacht wordt.

Daar isolatiemaatregelen, naast de gewenste effecten, ook negatieve effecten kunnen hebben voor de patiënt, is het van belang de criteria voor het opheffen van de isolatie helder in beeld te hebben zodat de isolatiemaatregelen niet langer duren dan noodzakelijk. Hier moet een multidisciplinaire afweging worden gemaakt.

Endemische fase

Sinds maart 2023 heeft Nederland de endemische fase m.b.t. SARS-CoV-2 bereikt. Het kabinet heeft op basis van dit advies de laatste nationale corona-adviezen (o.a. test- en isolatieadvies) laten vervallen. Dit is mogelijk omdat de afweer in Nederland inmiddels hoog is en weinig mensen ernstig ziek worden van de huidige virusvarianten. Het is wenselijk om ook de maatregelen in ziekenhuizen aan te passen om deze proportioneel te laten zijn ten opzichte van de ziektelast. Het European Center for Disease Prevention and Control heeft hierover ook een advies uitgebracht (ECDC 2023).

Rationale van de aanbeveling

De termijnen en de marges die in de aanbevelingen genoemd worden zijn gebaseerd op wetenschappelijke literatuur die tot nu toe beschikbaar is.

De aanbevelingen hebben betrekking op alle patiënten, zowel volwassenen als kinderen. Voor kinderen is echter minder data beschikbaar. De literatuursearch bij deze uitgangsvraag is algemeen ingezet. Studies met kinderen zijn niet geëxcludeerd. De aanbevelingen voor immuun gecompromitteerde patiënten zijn expert-based.

Onderbouwing

Achtergrond

In het verleden werd aangehouden dat een persoon met COVID-19 niet meer geïsoleerd hoeft te worden en volledig kan deelnemen aan de samenleving na 24 uur volledig symptoomvrij te zijn en tenminste 7 dagen na de eerste ziektedag (start klachten). Vervolgens werd de duur van isolatie in het landelijk beleid beperkt tot 5 dagen, met de voorwaarde van 24 uur klachtenvrij. De duur van 5 dagen isolatie betrof een (gedeeltelijk) pragmatische keuze vanwege de complexiteit om onderscheid te maken tussen diverse populaties. Sinds maart 2023 is er geen isolatieadvies meer van kracht.

Patiënten die opgenomen zijn (geweest) in het ziekenhuis kunnen ernstig ziek zijn geweest, een deel van hen is immuun gecompromitteerd en er moet rekening gehouden worden met kamer- en afdelingsgenoten. Er is daarom behoefte aan criteria voor ziekenhuizen om isolatie op te heffen/patiënten COVID-19 vrij te verklaren, en er komt langzaam meer informatie beschikbaar over de 'viral shedding' en de betekenis daarvan voor de besmettelijkheid van patiënten.

De adviezen beschreven in deze module zijn op basis van wetenschappelijke evidentie geformuleerd en betreffen patiënten.

Conclusies / Summary of Findings

Bij deze uitgangsvraag zijn geen conclusies geformuleerd.

Samenvatting literatuur

Bullard 2020, toonde in een retrospectieve cross-sectional studie aan dat SARS-CoV-2 uit positieve luchtweg monsters met een RT-PCR Ct waarde ≥ 24 en ≥ 8 dagen symptomen geen kweekbaar virus meer aangetoond kon worden wanneer deze geïnoculeerd werden op Vero cellen.

In totaal werden 90 monsters (nasopharynx en endotracheaal) geanalyseerd, afkomstig van Canadese COVID-19 patiënten, met een gemiddelde leeftijd van 45 jaar. De monsters werden verzameld tijdens routine surveillance en ingevroren totdat de kweek werd ingezet. De monsters in deze studie waren positief voor SARS-CoV-2 bevestigd met RT-PCR vanaf het begin van de symptomen (dag 0) tot 21 dagen na het begin van de symptomen. Tot 8 dagen na start symptomen werden positieve kweken waargenomen.

Multivariate logistische regressieanalyse waarbij een positieve kweek als voorspellende variabele werd meegenomen, toonde aan dat Ct-waarde significant geassocieerd was met de kweekresultaten (OR 0,64 95% BI 0,49-0,84, $p < 0,001$). Voor elke toename van de Ct-eenheid nam de kans (odds) op een positieve kweek met 36% af. De tijd tussen start van symptomen en testen (STT) was tevens significant geassocieerd met het kweek resultaat (OR 0,63, 95% BI 0,42-0,94, $p = 0,025$). Voor elke dag toename in STT, daalde de kans op een positieve kweek met 37%.

To 2020, toont SARS-CoV-2 aan in speeksel van 11/12 COVID19 bevestigde patiënten uit Hong Kong. De gemiddelde leeftijd was 62,5 jaar, 5 vrouwen en 7 mannen. Bij 6 patiënten werden meerdere speekselmonsters afgenomen. De frequentie wordt echter niet genoemd in de publicatie. SARS-CoV-2 werd aangetoond door middel van RT-PCR. Tevens werd het virus gekweekt door inoculatie op Vero cellen waarbij het cytopathische effect dagelijks, tot 7 dagen werd bekeken. Herhaalde monstername liet een afname zien in viral load na ziekenhuisopname. Bij 1 patiënt werd het virus 11 dagen na opname nog aangetoond met PCR. Ten tijde van publicatie waren kweek uitslagen positief voor 3 patiënten en negatief voor 2 patiënten. Het is niet beschreven welke monsters dit betrof en op welk tijdstip van ziekte de kweek is ingezet.

Wölfel 2020, toont actieve virusreplicatie aan in de bovenste luchtwegen bij 9 COVID-19 patiënten. Alle patiënten werden opgenomen in een ziekenhuis in München, Duitsland. Zowel voorafgaand als tijdens opname werden monsters afgenomen en onderzocht op aanwezigheid van het virus. Dit werd gedaan met behulp van PCR en viruskweek. Bij 50% van de patiënten trad seroconversie op na 7 dagen na start van symptomen en op 14 dagen bij alle patiënten. Na dag 8 kon geen virus meer worden gekweekt, ondanks nog hoge virale loads.

Vier studies uit de search update van 25 juni 2020 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Huang 2020, onderzocht de mogelijke correlatie tussen aantoonbaar viraal RNA m.b.v. RT-PCR en kweekbaar virus in klinische monsters van COVID-19 patiënten. Er werden 60 viruskweken uitgevoerd van monsters afkomstig van 50, met RT-PCR bevestigde, COVID-19 patiënten uit Taiwan. Het virus kon gekweekt worden uit 34 monsters, 12 keel, 9 nasopharynx en 2 sputum monsters. De Ct-waarden van de kweekbare en niet kweekbare monsters werden met elkaar vergeleken. De kweekbare monsters werden gekenmerkt door een significant lagere Ct-waarde voor alle drie de geteste genen (nsp12, E en N-gen). De hoogste Ct-waarde die voldoende was voor isolatie van het virus was Ct-waarde 31,47, 31,46 en 35,2 voor het nsp12, E- en N-gen, respectievelijk. De viral load werd verder geëvalueerd door het bestuderen van de genoomkopie aantallen van de 3 genen. Het laagste aantal kopieën dat vereist was voor virusisolatie, werd bepaald op 5,4, 6,0 en 5,7 log₁₀ genoomkopieën/ml monster voor het detecteren van respectievelijk het nsp12-, E- en N-gen. Monsters met kweekbaar virus worden gekenmerkt door hoge kopieaantallen.

De resultaten van dit onderzoek geven nieuwe inzichten in de besmettelijkheid van Covid-19 patiënten. Echter sampling bias door de afname van verschillende typen monsters, timing van verzameling en verschillende type opslag van monsters voorafgaand aan analyse (invriezen) en tevens de beperkte steekproefgrootte kunnen de resultaten van dit onderzoek hebben vertekend.

Van Kampen 2021, onderzocht in de periode 8 maart 2020 tot 8 april 2020 luchtwegmonsters (690) van 129 Covid-19 patiënten opgenomen in het Erasmus MC te Rotterdam, Nederland. Van deze patiënten werden er 89 patiënten (69,0%) opgenomen op de intensive care en 40 patiënten (31,0%) op de medium care. De monsters werden onderzocht met behulp van RT-PCR. Tevens werd de aanwezigheid van infectieus virus onderzocht met behulp van viruskweek. Bij 23 van de 129 patiënten (17,8%) werd besmettelijke virusuitscheiding gedetecteerd. De mediane duur van de uitscheiding was 8 dagen na het begin van de symptomen (IQR 5-11) en de waarschijnlijkheid dat het infectieuze virus werd opgespoord daalde tot minder dan 5% na 15,2 dagen na het begin van de symptomen (95% betrouwbaarheidsinterval (BI) 13,4 –

17,2). Multivariate analyses toonde een verband aan tussen de virale load boven 7 log₁₀ RNA-kopieën / ml en isolatie van infectieuze SARS-CoV-2 uit de luchtwegen (OR; BI 14,7 (3,57-58,1; p <0,001). Tevens was het aantonen van IgG en neutraliserende antistoffen voorspellend voor de afwezigheid van kweekbaar virus.

La Scola 2020, vonden een correlatie tussen Ct-waarden van de RT-PCR (E-gen) en het kunnen kweken van het virus. In het Méditerranée Infection University Hospital Institute te Marseille, Zuidoost-Frankrijk werden in totaal 183 monsters, afkomstig van 155 Covid-19 patiënten, geïnoculeerd in celculturen. Hieronder waren 9 sputummonsters en 174 nasopharynx monsters. Covid-19 was bevestigd door middel van RT-PCR gericht op het E-gen.

Van de 183 monsters kon uit 129 virus gekweekt worden. Hiervan hadden 124 monsters detecteerbaar cytopathisch effect tussen 24 en 96 uur. Er werd een significant verband gevonden tussen de Ct-waarde en het percentage positieve kweken. Monsters met Ct-waarden van 13–17 leidden allemaal tot positieve kweek. Het percentage positieve kweken nam vervolgens geleidelijk af tot 12% bij een Ct-waarde van 33. Er werden geen positieve kweken gevonden uit monsters met een hogere Ct-waarden dan 34.

Young 2020, onderzocht 100, met PCR bevestigde COVID-19 patiënten uit Singapore. Luchtwegmonsters (n=74) werden verzameld en met behulp van kweek geanalyseerd. Tevens werden serum en plasma monsters onderzocht op IgM/IgG niveaus, cytokines en chemokines. Er werd geen virus aangetoond bij PCR Ct waarden >30 of >14 dagen na start symptomen.

Vijf studies uit de search update van 6 november 2020 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Basile 2021, beschrijft de PCR en kweek resultaten van 195 COVID-19 patiënten (178 poliklinisch, 12 intramuraal, 5 IC). Alle met PCR bevestigde positieve monsters werden gekweekt in Vero C1008 cellen en dagelijks op cytopathisch effect (CPE) bekeken. CPE werd bevestigd met PCR op het supernatant. In totaal werden 234 monsters afgenomen waarvan 228 (97%) van de bovenste luchtwegen. SARS-CoV-2 werd alleen succesvol gekweekt van monsters met een Ct-waarde <32.

SARS-CoV-2 werd significant meer geïsoleerd van monsters afkomstig van IC- en intramurale patiënten dan van poliklinische patiënten en in monsters met lage Ct-waarden.

Gniazdowski 2021, beschrijft de resultaten van een retrospectief cohortonderzoek onder 2194 patiënten die herhaaldelijk zijn getest op COVID-19. (Data Johns Hopkins Hospital Microbiology laboratory –11 Maart tot 11 Mei 2020). In totaal zijn 29689 nasopharynx monsters van 2194 patiënten meegenomen in de analyse. 17% testte positief met PCR. WGS werd toegepast om het virus genotype te bevestigen in patiënten met herhaaldelijke vaststelling van viraal RNA.

Positieve viruskweek werd gevonden in monsters met een CT-waarde van gemiddeld 18.8 ± 3.4 . Langdurige virale RNA-uitscheiding was geassocieerd met positieve viruskweek in monsters tot 22 dagen na het eerste positieve resultaat. Meestal waren patiënten symptomatisch op het moment van monsterafname. Volledige genomesequentiebepaling leverde bewijs dat hetzelfde virus in de loop van de tijd werd overgedragen. Positieve PCR uitslagen na een eerdere negatieve uitslag hadden Ct-waarden hoger dan 29,5 en waren niet geassocieerd met een positieve viruskweek.

Laferl 2021, beschrijft de resultaten van 15 gezonde gezondheidsmedewerkers uit Oostenrijk die niet werkten vanwege aanhoudende positieve RT-PCR resultaten in nasofaryngeale (NP) en orofaryngeale (OP) uitstrijken na een COVID-19 infectie. De populatie bestond uit 4 vrouwen en 11 mannen, met een gemiddelde leeftijd van 41 jaar (22-59 jaar). Geen van de deelnemers was opgenomen geweest tijdens de COVID-19 infectie. Twee personen waren asymptomatisch en 13 personen hadden milde klachten. Van iedere deelnemer werden NP, OP en bloedmonsters verzameld. PCR en kweek werd uitgevoerd op de afgenomen NP en OP monsters en serumneutralisatietest en ELISA werd uitgevoerd op de serummonsters. Er werd geen positieve viruskweek gevonden. RT-PCR Ct waarden waren gemiddeld 37.4; median 37.3; range 30.8–41.7. IgG werd in alle 15 personen aangetoond. Neutraliserende antistoffen werden gevonden in 7/15 personen bij de eerste monsternamen in 14/15 bij de tweede afname.

Sohn 2020, beschrijft de resultaten van 48 asymptomatische of mild symptomatische COVID-19-patiënten bij wie de ziekte was vastgesteld minimaal twee weken voorafgaand aan monsternamen. De patiënten bestonden uit 14 mannen en 24 vrouwen met een gemiddelde leeftijd van 32,6 jaar (± 14.59). Van deze patiënten waren er 11 asymptomatisch. Van iedere patiënt werden nasofarynx en speeksel swabs afgenomen. Deze werden onderzocht met PCR en kweek. Ondanks positieve PCR resultaten (gemiddelde CT 33.7 en 33.8 voor nasofarynx swabs en keel swabs respectievelijk) werden geen positieve kweken gevonden.

Walsh 2020, geeft een overzicht van de verschenen publicaties tussen 1 januari en 26 augustus 2020 m.b.t. de duur van de besmettelijkheid SARS-CoV-2 positieve personen. Er werden 15 relevante onderzoeken gevonden waaronder in 13 studies viruskweek werd toegepast.

Voor 5 viruskweekstudies vond de laatste dag waarop SARS-CoV-2 werd geïsoleerd plaats binnen 10 dagen na het begin van de symptomen. Voor nog eens 5 onderzoeken werd SARS-CoV-2 na dag 10 geïsoleerd voor ongeveer 3% van de geïncubeerde patiënten. De overige 3 viruskweekstudies omvatten patiënten met een ernstige of kritieke ziekte; In één onderzoek werd SARS-CoV-2 tot dag 32 geïsoleerd. Twee studies toonden in immuun gecompromitteerde patiënten SARS-CoV-2 aan in viruskweek tot 20 dagen na start van symptomen.

Op basis van de geïncubeerde studies concludeert Walsh dat het zeer onwaarschijnlijk is dat COVID-19-patiënten met een milde tot matige klachten besmettelijk zijn na 10 dagen na de start van de symptomen. Uit een beperkt aantal onderzoeken blijkt echter dat patiënten met ernstige tot kritieke ziekte of die immuun gecompromitteerd zijn, het infectieuze virus langer kunnen uitscheiden.

Drie studies uit de search update van 2 februari 2021 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Aydillo 2020 onderzocht de duur van de besmettelijkheid onder 20 immuun-gecompromitteerde Covid-19 patiënten in de eerste golf. Van de geïncubeerde patiënten ontvingen er 18 stamcel- of CAR T-cel therapie en 2 patiënten hadden een lymfoom. Van de 20 patiënten kregen er 15 een behandeling of chemotherapie. Elf patiënten hadden ernstige Covid-19.

Nasopharynx en sputum swabs werden herhaaldelijk afgenomen voor RT-PCR en kweek. Viraal RNA werd tot 78 dagen na het begin van de symptomen (IQR, 24 tot 64 dagen) aangetoond. Kweekbaar virus werd gedetecteerd in 10 van de 14 nasofaryngeale monsters (71%) die beschikbaar waren vanaf de eerste dag van

testen. In follow-up monsters verkregen van 5 patiënten groeide virus in de kweek gedurende 8, 17, 25, 26 en 61 dagen na het begin van de symptomen.

Li 2020 onderzocht de klinische en virale eigenschappen van 38 Covid-19 patiënten die langdurig drager waren van het virus. De patiënten waren hersteld van de acute ziekte, maar scheidden nog steeds viraal RNA uit (mediaan 92 dagen – langste 118 dagen na opname). Er werden fluctuaties in uitscheiding waargenomen (negatief/positief). Langdurige dragers waren voornamelijk ouderen met een milde infectie. Infectieus virus werd aangetoond in kweken van sputum monsters met hoge virale load. Er werden positieve kweken gevonden in 2/16 sputum monsters bij een CT waarde 26-27 op dag 73 en 102. Patiënten hadden slechts geringe/geen klachten meer maar nog afwijkingen waarneembaar op CT.

Tevens werd de antistof respons gemeten en vergeleken met een groep van 60 personen die tenminste 28 dagen hersteld waren van Covid-19 en een groep gezonde personen. IgM- en IgG-antilichamen en de profielen van neutraliserende antilichamen waren vergelijkbaar met de groep patiënten die volledig hersteld waren. Ondanks dat Covid-19 patiënten neutraliserende antilichamen vormen kunnen ze toch langdurig SARS-CoV-2 blijven uitscheiden.

Manzulli 2021, onderzocht de virale klaring met behulp van viruskweek bij ziekenhuis opgenomen patiënten die klinisch hersteld waren van Covid-19, maar nog steeds positief testte op de nasofarynx-swab (RT-PCR). In totaal werden 83 patiënten onderzocht. De geïnccludeerde patiënten varieerde van asymptomatisch tot ernstig ziek en hadden een gemiddelde leeftijd van 46 jaar $\pm$ 20,29. In 40,5% van de proefpersonen was longontsteking radiologisch bevestigd. Alle patiënten ondergingen een nasofarynx controle-swab op dag 14 voor asymptomatische patiënten of drie dagen na remissie van symptomen bij patiënten met ernstigere symptomen. RT-PCR-positieve monsters werden gekweekt. Er werden geen positieve viruskweken gevonden. Deze resultaten tonen aan dat patiënten die gedurende ten minste drie dagen klinisch hersteld zijn, op basis van virale kweek vermoedelijk niet meer besmettelijk zijn.

Zes studies uit de search update van 18 mei 2021 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Bellon 2021 toont aan dat "SARS-CoV-2 viral load (VL) kan dienen als een correlaat voor de aanwezigheid van infectieus virus en virus overdracht. Er werd gekeken naar de kinetiek van virale uitscheiding gedurende de eerste week van ziekte bij symptomatische kinderen (n=279), adolescenten (n=639) en volwassenen (n=7109). VL werden berekend op basis van het E-gene target. De deelnemers vertonen VL's die overeenkomen met de aanwezigheid van infectieus virus. Hierbij hebben kinderen een iets lagere VL dan volwassenen, echter is dit verschil niet significant verschillend. Infectieus virus kon worden aangetoond bij VL's van 6 log₁₀ SARS-CoV-2 copies/mL.

Benotmane 2021 onderzocht de duur van kweekbaar SARS-CoV-2-uitscheiding bij patiënten die een niertransplantatie hebben ondergaan. In totaal werden (retrospectief) 40 nasofaryngeale monsters van 16 SARS-CoV-2 RT-PCR-positieve niertransplantatie patiënten onderzocht m.b.t. celkweek tot 39 dagen vanaf het begin van symptomen. In 25% van de monsters werd kweekbaar SARS-CoV-2-aangetoond tot 3 weken vanaf het begin van de symptomen.

Laferl 2021 onderzocht 40 gezonde zorgmedewerkers die vanwege aanhoudende positieve SARS-CoV-2 RT-PCR-resultaten in thuisquarantaine verbleven. Deelnemers hadden milde klachten. Van alle deelnemers werden nasofaryngeale, orofaryngeale swabs en een bloedmonster afgenomen. De swabs werden onderzocht met RT-PCR en viruskweek. Van het bloedmonster werd een serumneutralisatietest, evenals twee verschillende ELISA-tests uitgevoerd.

Kweekbaar virus kon in geen van de onderzochte monsters worden aangetoond. Ct-waarden in RT-PCR waren gemiddelde 37,4; mediaan 37,3; range 30,8–41,7. Op één na werden in alle deelnemers neutraliserende antilichamen aangetoond in gelijktijdig afgenomen bloedmonsters.

Owusu 2021 onderzocht de uitscheiding en infectiviteit van 109 personen met RT-PCR-bevestigde COVID-19. De deelnemers hadden milde tot matige Covid-19 klachten en werden herhaaldelijk getest. Viruskweek werd toegepast vanaf dag 10 na de start van symptomen. Er werd geen kweekbaar virus aangetoond na dag 10 in de onderzochte monsters (10 dagen na start symptomen).

Sonnleitner 2021 beschrijft de resultaten van een in vitro studie waarbij 109 oropharyngeale monsters (verkregen uit routine testen) werden onderzocht met behulp van RT-PCR, viruskweek en virus titratie. Er werd een negatieve correlatie ($r = -0.76$; $p < 0.05$) gevonden tussen de uitkomst van RT-PCR en de kans op een succesvolle isolatie uit de kweek en titratie. De kans op het vinden van kweekbaar virus bij een Ct waarde boven de 30 bleek zeer klein.

Yamada 2021 onderzocht de correlatie tussen virale load (RT-PCR) en celkweek resultaten van 203 SARS-CoV-2 positieve bovenste luchtweg monsters. Hierbij werd gebruik gemaakt van een N2 primer/probe set welke is ontwikkeld voor het testen op Covid-19 in Japan.

In monsters met een Ct-waarden onder 20.2 kon kweekbaar virus aangetoond worden. Echter werd ook in 6,9% van de monsters met Ct-waarden >35 virus aangetoond in de kweek.

Vijf studies uit de search update van 18 november 2021 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Glans (2021) investigated 36 hospitalized patients. From patients displaying SARS-CoV-2 specific IgG titer above 40, or neutralizing antibodies above 10, no viable virus could be cultured, despite RT-PCR results being positive. Suggesting serological assays might be helpful in determining infectiousness of patients.

Folgueira (2021) included 189 patients, of whom 11 were asymptomatic. Viral viability was maintained for up to 10 days in patients with mild COVID-19. In patients with severe COVID-19, the virus remained viable for up to 32 days after the onset of symptoms. Patients with severe COVID-19 presented infectious virus at a significantly higher rate in the samples with moderate to low viral load (cycle threshold value > 26): 32/75 (43%) versus 14/63 (22%) for mild cases ($p < 0.01$). We observed a positive CPE despite the presence of clear neutralizing activity ($NT_{50} > 1:1024$ in 10% (3/30) of samples).

Ke (pre-print 2021) investigated 23 individuals at varying stages of vaccination infected with SARS-CoV-2 variants B.1.1.7 (Alpha) and P.1 (Gamma), by using nasal and saliva swabs RT-PCR tests and viral culture. Vaccinated individuals had significantly lower days of positive viral culture, compared to newly vaccinated

($p < 0.05$) and non-vaccinated individuals ($p < 0.001$). Vaccinated individuals also had significantly lower days of symptoms compared to unvaccinated individuals ($p < 0.05$). Furthermore, for Ct/Cn values < 27 , the probability for positive viral culture was lower for vaccinated versus newly and unvaccinated individuals (although not significant due to small number of fully vaccinated participants ($n = 6$)).

Murata (2021) investigated a cruiseship cohort of asymptomatic individuals ($n = 90$). Samples with positive culture were obtained from 7 carriers with a median age of 71 (IQR, 66 to 74; range, 60 to 77), 5 of whom were female. The last positive cytopathic effect (CPE) was observed in samples collected a median of 7 days (IQR, 6 to 7; range, 6 to 15) after the initial positive PCR test (day 0).

The median crossing point (Cp) value of RT-PCR of culture-positive samples was 24.6 (IQR 20.4 to 25.8; range 17.9 to 30.3), and Cp values were significantly associated with isolation of viable virus (OR 0.496; 95%CI 0.329 to 0.747; P-value 0.001).

Nomura (2021) investigated 23 patients with severe COVID-19 who required mechanical ventilation, all with comorbidities. Seven patients were culture positive with a median conversion time of 14 days, with one patient having a conversion time of 24 days. PCR testing revealed viral loads of at least 104 copies/mL, even in specimens with a negative viral culture test result.

Singanayagam (2020) investigated the duration of infectiousness in persons who test positive for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) by understanding how RT-PCR detection relates to cultivable virus. Upper respiratory tract (URT) samples from persons with suspected COVID-19 (late January to early April 2020) were tested at the national respiratory virus reference laboratory at Public Health England to support routine clinical care and surveillance activities during the COVID-19 pandemic. Samples included nose, throat, combined nose-and-throat and nasopharyngeal swabs, or nasopharyngeal aspirates; the majority were taken by clinical staff but some were self-sampled nose swabs. Virus culture was attempted from 324 URT samples (from 253 cases) that tested positive for SARS-CoV-2 by RT-PCR. Samples were obtained from a range of clinical scenarios including community and healthcare worker surveillance, symptomatic persons tested as part of the early epidemic response and samples acquired in outbreak investigations.

Severe acute respiratory syndrome coronavirus 2 viral load in the upper respiratory tract peaks around symptom onset and infectious virus persists for 10 days in mild-to-moderate coronavirus disease ($n = 324$ samples analysed). RT-PCR cycle threshold (Ct) values correlate strongly with cultivable virus. Probability of culturing virus declines to 8% in samples with Ct > 35 and to 6% 10 days after onset; it is similar in asymptomatic and symptomatic persons.

Zes studies uit de search update van 10 februari 2022 werden opgenomen in de literatuuranalyse en zijn hieronder samengevat.

Boucau (pre-print 2021) studied viral culture dynamics post-treatment in 69 participants receiving the monoclonal antibody bamlanivimab or a placebo in the ACTIV-2 trial. Of the 69 participants meeting inclusion criteria, 39 participants fell into the placebo arm and 30 participants fell into the bamlanivimab arm (20 received the 7000mg dose and 10 received the 700mg dose). Baseline participant characteristics, including age, race, comorbidities, days of symptoms before enrollment, serostatus, and baseline anterior nasal viral load were similar between groups. Baseline viral culturability, as determined by cytopathic effect (CPE), was

also similar between groups, with 39/39 (100%) participants in the placebo arm and 28/30 (93%) participants in the mAb arm with culture positive baseline sample. Viral load by qPCR and viral culture were performed from anterior nasal swabs collected on study days 0 (day of treatment), 1, 2, 3, and 7. Treatment with mAb resulted in rapid clearance of culturable virus in participants without treatment-emergent resistance. One day after treatment, 0 of 28 (0%) participants receiving mAb and 16 of 39 (41%) receiving placebo still had culturable virus ($p < 0.0001$). By day 2 post-treatment, 7 of 39 (18%) participants in the placebo arm were still culture positive; all participants in the bamlanivimab arm remained culture negative. 15 participants in the placebo arm and 0 participants in the bamlanivimab arm were culture positive at study day 1 and/or 2 and underwent additional testing on samples from days 3 and 7. Day 3, five of 15 tested placebo participants remained culture positive, and on study day 7, one of 15 tested placebo participants remained culture positive.

Siedner (2022) followed a cohort of 24 (10 delta variant, 4 alpha, 1 gamma, 1 mu, 8 unknown) ambulatory patients with postvaccination breakthrough SARS-CoV-2 infections with longitudinal collection of nasal swabs for SARS-CoV-2 viral load quantification, whole-genome sequencing, and viral culture. The mean age was 46 years (SD14) for patients with delta variant infections and 41 years (SD 16) for patients with non-delta/predelta variants. Home visits 3 times weekly were conducted until negative PCR testing. At each visit, self-collected nasal swabs for SARS-CoV-2 PCR, culture, and whole-genome sequencing were obtained. All delta variant infections in the cohort were symptomatic, compared with 64% of non-delta variant infections.

Delta variant postvaccine breakthrough infections were more likely to grow in culture than alternate variants infections (7 of 10 [70%] vs. 3 of 14 [23%] infections, $P = 0.035$). This pattern was consistent when restricted to symptomatic infections only (7 of 10 [70%] vs. 3 of 9 [33%] infections, $P = 0.179$).

Individuals with delta variant infections had slower viral load decay, as assessed by PCR (median time, 13.5 vs. 4.5 days; HR, 0.38; 95% CI, 0.15, 0.95). Delta variant infection was also associated with lower hazard of conversion to negative viral culture (HR, 0.43; 95% CI 0.18, 1.03), although the difference in median time to negative viral culture was less pronounced than it was for conversion to negative PCR (median time to negative viral load, 7 vs. 4 days). Nine of 10 (90%) individuals with delta variant postvaccine breakthrough infections had a confirmed negative viral culture within 10 days of symptom onset. The remaining participant had culturable virus at day 11 but a negative culture at day 13. That participant remained symptomatic at day 11.

Time to negative viral load by PCR was longer for individuals infected more than 3 months after completion of vaccination compared with those infected within 3 months of vaccination (median time, 13.5 vs. 3 days; HR, 0.20; 95% CI, 0.08, 0.53; Figure 2C), with a significant, albeit diminished, difference in time to negative viral culture (median time, 7 vs. 3 days; HR, 0.40; 95% CI, 0.17, 0.93).

Salvatore (2021) assessed markers of viral shedding in vaccinated and unvaccinated persons during a SARS-CoV-2 Delta variant outbreak among incarcerated persons in a federal prison in Texas.

Consenting persons with confirmed SARS-CoV-2 infection provided mid-turbinate nasal specimens daily for 10 consecutive days and reported symptom data via questionnaire. Real-time reverse transcription-polymerase chain reaction (RT-PCR), viral whole genome sequencing, and viral culture was performed on these nasal specimens. Duration of RT-PCR positivity and viral culture positivity was assessed using survival analysis.

A total of 978 specimens were provided by 95 participants, of whom 78 (82%) were fully vaccinated and 17

(18%) were not fully vaccinated. Of the 978 specimens collected, viral culture was performed on 286 (29%). Specimens were included for viral culture if they had been collected 0, 3, 5, 7, or 9 days since onset and had an accompanying positive RT-PCR test with cycle threshold (Ct) value less than 35. No significant differences were detected in duration of RT-PCR positivity among fully vaccinated participants (median: 13 days) versus those not fully vaccinated (median: 13 days; $p=0.50$), or in duration of culture positivity (medians: 5 days and 5 days; $p=0.29$). Among fully vaccinated participants, overall duration of culture positivity was shorter among Moderna vaccine recipients versus Pfizer ($p=0.048$) or Janssen ($p=0.003$) vaccine recipients. No statistically significant differences in duration of culture positivity were detected when stratified according to time since vaccination ($p=0.79$) or known prior infection ($p=0.99$).

Note: this article is a pre-print and has not been peer-reviewed yet.

Glenet (2021) included 496 COVID-19 patients, including 180 asymptomatic patients. Of these adult asymptomatic viral shedders, 75% had mean to high RNA viral loads (Ct values < 30) which median value was significantly higher than that observed in symptomatic subjects ($P = 0.029$), and 50.6% were positive by cell culture assays of their upper respiratory tract specimens. 135 asymptomatic subjects had RT-PCR Ct-values lower than 30 and 45 subjects had RT-PCR Ct values upper than 30. A strong correlation was found ($R^2 = 0.591$, $P < 0.0001$) between initial SARS-CoV-2 RT-PCR Ct-values in respiratory specimens and fold increase of viral RNA levels following viral culture of the same samples. Among studied asymptomatic patients, 50.6% of them were characterized by the presence of viable virus associated with RT-PCR Ct-values lower than 30 in their respiratory specimens, whereas 39.76% of them evidenced no viable viral particles despite RT-PCR Ct-values lower than 30 in their respiratory specimens. None of the asymptomatic patients with RT-PCR Ct-values higher than 30 in their upper respiratory tract demonstrated the presence of detectable replicative viral particles.

Fall (pre-print 2022) investigated Delta variant with Omicron variant by obtaining clinical outcomes, Ct-values, viral cultures, and levels of respiratory IgG. 1121 patients with Omicron were included, next to 910 patients with Delta. Of the vaccinated participants, 68.6% received Pfizer/BioNTech, 1273 (26.6%) Moderna mRNA-, and 149 (4.8%) the J&J/Janssen COVID-19 vaccine. Patients with Omicron were more likely to be vaccinated, but regardless of vaccination status, they were less likely to be admitted, succumb to infection, and require ICU care. Furthermore, regardless of vaccination status, no statistically significant difference was observed in Ct-values. In patients with Delta infection, vaccination reduced infectious viral culture if patients were boosted compared to fully vaccinated (without booster) and unvaccinated individuals (62% vs 87 and 82 %, $p=0.009$ and 0.04). In Omicron, vaccination status did not alter recovery of infectious virus (55%, 69%, and 60%, NS) (Delta 78% vs Omicron 61%; $p = 0.0006$).

Note: this article is a pre-print and has not been peer-reviewed yet.

Yonker (2021) assessed respiratory swabs from 110 children with COVID-19. Median age was 10 years (range 2 weeks–21 years), 56% were boys and 30 children were asymptomatic. RT-PCR, viral culture, and genome sequence were analyzed once. Asymptomatic cases were younger than moderate/severe cases. Viral load was significantly higher in children with asymptomatic and mild disease compared to hospitalized adults ($P<0.0001$). However, viral load of hospitalized children with moderate/severe disease was not significantly lower than in hospitalized adults. Age was not correlated with viral load in any group of severity (Pearson correlation: $r = -0.1$, 0.01 , and -0.2 , respectively; $P = \text{ns}$). Furthermore, viral clearance was also not significantly different between severity groups in children, nor adults. Viral culture was positive in 32 of 110

patients, of which 8 were asymptomatic. Higher viral load was associated with positive viral culture ($p < 0.0001$). Children were most infectious within first 5 days of disease, with viral load being at its highest in the first 2 days of symptoms. Positive viral culture was most likely when performed early after symptom onset ($P = 0.004$). Viral genome sequencing revealed 4 Alpha (B.1.1.7) variants and 3 Iota (B.1.526.2) variants.

Eén studie uit de search update van maart 2023 werden opgenomen in de literatuuranalyse en is hieronder samengevat.

Wu (2023) conducted a systematic review of to assess the duration of viable virus shedding and polymerase chain reaction (PCR) positivity of the SARS-CoV-2 Omicron variant in the upper respiratory tract. PubMed, Cochrane, and Web of Science were systematically searched for original articles reporting the duration of viable virus shedding and PCR positivity of the SARS-CoV-2 Omicron variant in the upper respiratory tract from November 11, 2021 to December 11, 2022. This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered with PROSPERO (CRD42022357349). DerSimonian-Laird random-effects meta-analysis was used to obtain the pooled value and the 95% confidence intervals. In total 29 studies (of which 2 were pre-prints) and 230,227 patients were included. In 11 studies data on viable virus shedding was reported. The pooled duration of viable virus shedding of the SARS-CoV-2 Omicron variant in the upper respiratory tract was 5.16 days (95% CI: 4.18-6.14), and the average duration of PCR positivity was 10.82 days (95% CI: 10.23-11.42). The duration of viable virus shedding and PCR positivity of the SARS-CoV-2 Omicron variant in symptomatic patients was slightly higher than that in asymptomatic patients, but the difference was not significant ($P > 0.05$). Based on data from 10 patients (symptomatic, eight; asymptomatic, two): the duration of viable virus shedding was similar between symptomatic and asymptomatic patients (6.25 vs 5.00 days, respectively; $P > 0.05$).

Bewijskracht van de literatuur

De literatuur betreft hoofdzakelijk niet vergelijkend onderzoek. Om deze reden heeft er geen beoordeling van de bewijskracht plaatsgevonden en zijn er geen conclusie geformuleerd.

Zoeken en selecteren

Om de uitgangsvraag te kunnen beantwoorden is er een systematische literatuuranalyse verricht naar de volgende zoekvraag: Wanneer is een COVID-19 patiënt niet meer besmettelijk en kunnen isolatiemaatregelen worden opgeheven? Tot hoeveel dagen na start van symptomen is er infectieus (kweekbaar) virus aantoonbaar in de COVID-19 patiënt?

P: Patiënten met bevestigde COVID-19 infectie

I: -

C: -

O: Aantal dagen waarbij infectieus virus kan worden aangetoond na start symptomen

Relevante uitkomstmaten

De werkgroep achtte het aan tonen van kweekbaar virus een voor de besluitvorming cruciale uitkomstmaat. De werkgroep definieerde niet a priori de genoemde uitkomstmaten, maar hanteerde de in de studies

gebruikte definities. Kweekbaar virus is tot nu toe de beste proxy voor het meten van infectieus virus en daarmee de kans op transmissie. Hierbij erkent de werkgroep dat de kans op transmissie ook samenhangt met eventuele (rest)klachten als hoesten en niezen, en dat het geen gegeven is dat met kweekbaar virus ook de minimale infectieuze dosis wordt bereikt.

Zoeken en selecteren (Methode)

In de databases PubMed, Embase, Google Scholar, WHO en Medrxiv is op 26 mei 2020 met relevante zoektermen gezocht naar studies waarbij gekeken is naar de aan- of afwezigheid en duur van kweekbaar virus; virus shedding en viral load van SARS-Cov-2 bij COVID19 patiënten. De zoekverantwoording is weergegeven onder het tabblad Verantwoording. De literatuurzoekactie leverde 417 treffers op. Studies werden geselecteerd op grond van de volgende selectiecriteria: inclusie van patiënten met bevestigde COVID-19 infectie – waarbij in seriële monsternamen gekeken is naar de duur van uitscheiding van SARS-CoV-2 en de aanwezigheid van kweekbaar virus.

Op basis van titel en abstract werden in eerste instantie 56 studies voorgeselecteerd. Na raadpleging van de volledige tekst, werden vervolgens 54 studies geëxcludeerd (zie exclusietabel onder het tabblad Verantwoording) en 2 studies definitief geselecteerd.

Op 25 juni 2020 is er opnieuw gezocht naar studies waarbij gekeken is naar aan- of afwezigheid en duur van kweekbaar virus; virus shedding en viral load van SARS-Cov-2 bij COVID19 patiënten. De zoekstrategie is hierbij nog meer specifiek ingezet op studies die virus hebben gekweekt. De zoekverantwoording is weergegeven onder het tabblad Verantwoording. De literatuurzoekactie leverde 49 nieuwe treffers op. Studies werden geselecteerd op grond van de hierboven genoemde selectiecriteria. Op basis van titel en abstract werden in eerste instantie 5 studies voorgeselecteerd. Na raadpleging van de volledige tekst, werden vervolgens 2 studies geëxcludeerd (zie exclusietabel onder het tabblad Evidence Tabellen) en 2 studies definitief geselecteerd. Tevens werd 1 extra studie geïncludeerd (van Kampen, 2021), een pre-print publicatie.

Op 6 november 2020, 2 februari 2021, 18 mei 2021, 18 november 2021, 10 februari 2022 en 24 maart 2023 is gezocht in de databases PubMed, Embase, Google Scholar, WHO en Medrxiv met behulp van bovenstaande zoekstrategie. Studies werden geselecteerd op grond van de volgende selectiecriteria: inclusie van patiënten met bevestigde COVID-19 infectie – waarbij in seriële monsternamen gekeken is naar de duur van uitscheiding van SARS-CoV-2 en de aanwezigheid van levend virus werd bevestigd. Daarnaast is specifiek gelet op de correlatie tussen positieve virusweek en Ct-waarde van PCR. De literatuurzoekactie van 6 november 2020 leverde 116 nieuwe treffers op, waarvan op basis van titel en abstract 5 studies definitief werden geselecteerd. De literatuurzoekactie van 2 februari 2021 leverde 797 nieuwe treffers op, waarvan op basis van titel en abstract 3 studies definitief werden geselecteerd. De literatuurzoekactie van 18 mei 2021 leverde 593 nieuwe treffers op, waarvan op basis van titel en abstract 6 studies definitief werden geselecteerd. De literatuurzoekactie van 18 november 2021 leverde 1733 nieuwe treffers op, waarvan op basis van titel en abstract 6 studies definitief werden geselecteerd. De literatuurzoekactie van 10 februari 2022 leverde 1110 nieuwe treffers op, waarvan op basis van titel en abstract 3 studies definitief werden geselecteerd. De literatuurzoekactie van 24 maart 2023 leverde 441 nieuwe treffers op, waarvan op basis van titel en abstract 1 studie definitief werden geselecteerd.

Resultaten

In totaal werden er 30 studies definitief geselecteerd en hieronder samengevat.

Verantwoording

Laatst beoordeeld : 10-01-2024

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Diagnostiek bij COVID -19

Waar gaan de modules binnen deze richtlijn over?

De modules Diagnostiek binnen de richtlijn COVID19 richten zich op wat volgens de huidige maatstaven de beste diagnostiek is voor patiënten met COVID-19. De volgende onderwerpen komen aan de orde:

- Klinische karakteristieken voorspellend voor COVID-19
- Aanvullende diagnostiek na negatieve PCR-test
- Serologie na vaccinatie of herinfectie
- Preoperatieve screening naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie

Voor wie zijn deze richtlijnmodules bedoeld?

Deze modules zijn ontwikkeld voor alle leden van de beroepsgroepen die betrokken zijn bij COVID-19 diagnostiek.

Voor patiënten

Deze modules helpen artsen in het stellen van een COVID19 diagnose binnen het ziekenhuis.

Voor patiënten is op Thuisarts.nl informatie te vinden over COVID-19 (<https://www.thuisarts.nl/corona>).

Hoe zijn de richtlijnmodules tot stand gekomen?

Deze modules zijn in 2021 ontwikkeld op initiatief van de Federatie Medisch Specialisten. De modules zijn opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit de internisten, arts-microbiologen, longartsen, radiologen, chirurgen, anesthesiologen en kinderartsen.

Bij meerdere modules is gebruik gemaakt van reeds ontwikkelde documenten, zoals de 'Leidraad diagnostiek bij patiënten met een opname-indicatie en verdenking COVID-19 infectie' (Expertiseteam Diagnostiek, 2021) en 'Pre-operatieve screening naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie' (Werkgroep Preoperatieve Screening SARS-CoV-2, Expertiseteam Diagnostiek, 2021). Dit wordt in de betreffende modules nader toegelicht.

Toepassen

Bij de module 'Preoperatieve screening naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie' is een stroomschema gemaakt.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Klinische karakteristieken voorspellend voor COVID-19

Uitgangsvraag

Welke klinische symptomen (typisch en atypisch) zijn sterk voorspellend voor een COVID-19 diagnose?

Aanbeveling

Wees alert op COVID-19 bij onderstaande symptomen:

Meest voorkomende symptomen passend bij COVID-19 zijn:

- Hoesten
- Benauwdheid
- Verhoging of koorts

Andere veelvoorkomende symptomen passend bij COVID-19 zijn:

- Rillerigheid
- Vermoeidheid
- Spierpijn
- Hoofdpijn
- Keelpijn
- Plotseling verlies van reuk en/of smaak (zonder neusverstopping)
- Rhinorrhoe
- Misselijkheid of overgeven
- Diarree

Houd bij het inschatten van de waarschijnlijkheid van COVID-19 rekening met de actuele prevalentie van COVID-19 in de samenleving.

Wees alert op COVID-19 in geval van plotseling smaak- en reukverlies zonder neusverstopping.

Wees alert op de vaak atypische presentatie van COVID-19 bij ouderen en kinderen.

Ouderen presenteren zich vaak met delier (hypoactief), vallen, hypothermie of gastro-intestinale klachten.

Kinderen en adolescenten kunnen na een acute SARS-CoV-2 infectie symptomen vertonen die lijken op die van de ziekte van Kawasaki of Guillain Barré: paediatric multisystem inflammatory syndrome temporally related to SARS-CoV-2' (PIMS-TS).

Overwegingen

Kwaliteit van het bewijs

Er was een zeer lage bewijskracht van de positief voorspellende waarde van enkele specifieke klinische symptomen voor de diagnose COVID-19. Er zijn weinig studies gevonden waarin de sensitiviteit, specificiteit en voorspellende waarde van specifieke klinische symptomen is onderzocht. Daarnaast hebben de beschikbare studies veel beperkingen in studieopzet en vaak kleine patiëntaantallen.

Vier studies en een systematische review beschrijven de voorspellende waarde van enkele klinische symptomen waaronder het verlies van reuk en smaak en diarree. De positief voorspellende waarde van de aanwezigheid van het verlies van geur en/ of smaak was niet erg hoog en varieerde van 0,32 tot 0,80. De specificiteit was wel redelijk hoog en varieerde van 0,89 – 0,99. De voorspellende waarde van diarree was niet hoog.

Ouderen

We hebben geen studies gevonden over de voorspellende waarde van atypische symptomen bij ouderen of kinderen. Wel zijn er studies die de meest voorkomende klachten bij specifieke patiëntenpopulatie, waaronder ouderen en kinderen en adolescenten, rapporteren.

Studies beschrijven dat COVID-19 bij kwetsbare ouderen vaak atypisch verloopt. Retrospectieve studies naar de klachten bij presentatie van ouderen en verpleeghuispatiënten tonen aan dat oudere patiënten (65 jaar of ouder) in tot 40-100% van de gevallen atypische presentaties kunnen hebben (Gan, 2020). Ze presenteren zich vaak met een delier (22-67%) - met name hypoactief delier dat wordt gekenmerkt door apathisch, teruggetrokken gedrag en een verminderde alertheid, vallen (10-37%), hypothermie (34%) en maag-darmklachten (4-19%). Het advies is om ouderen laagdrempelig te testen op COVID-19 bij aanwezigheid van atypische symptomen.

De mate waarin ouderen zich presenteren met atypische klachten hangt echter meer af van de kwetsbaarheid dan van de leeftijd (Olde Rikkert, 2020). Een kwetsbaar iemand van 60 jaar kan zich atypischer presenteren dan een vitaal iemand van 75 jaar. Kwetsbaarheid is geassocieerd met hogere kans op sterfte bij oudere COVID-19-patiënten in het ziekenhuis (Blomaard, 2021).

De Clinical Frailty Scale is tijdens de corona-pandemie in veel ziekenhuizen gebruikt om in te schatten of een oudere baat zou kunnen hebben bij behandeling op de IC voor COVID-19. Kwetsbaarheid bij een oudere patiënt wordt door een klinisch geriater of internist-ouderengeneeskunde vastgesteld middels het Comprehensive Geriatric Assessment (CGA). Voor screening op kwetsbaarheid worden in het ziekenhuis diverse instrumenten gebruikt zoals de APOP op de SEH en de VMS kwetsbare ouderen criteria of de ISAR-HP bij opname in het ziekenhuis..

Kinderen en adolescenten

Symptomen van een SARS-CoV-2 infectie in kinderen kunnen aspecifiek zijn (Swann, 2020; Garazzino, 2020; Christopers, 2020). Klassieke klachten zoals koorts en luchtweg kunnen op treden, maar dat is zeker niet altijd zo. Opvallend vaak is er sprake van gastro-intestinale klachten, aspecifieke huidbeelden of zijn er geen klachten. Het is onmogelijk om o.b.v. klinische parameters acute SARS-COV 2 infecties te onderscheiden van ander virale verwekkers. Kinderen en adolescenten kunnen in het ziekenhuis symptomen vertonen die lijken op die van de ziekte van Kawasaki of Guillain Barre na acuut COVID-19, wat aanleiding kan geven tot

overweging van het Multisystem Inflammatory Syndrome (MIS-C). Deze klinische uiting wordt nu omschreven als 'paediatric multisystem inflammatory syndrome temporally related to SARS-CoV-2' (PIMS-TS). Deze diagnose komt in deze richtlijn niet aan de orde.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

De diagnostiek kan voor patiënten ongemakkelijk zijn (nasofaryngeaal SWAB, bloedafname). Fout negatieve testuitslagen kunnen leiden tot verspreiding van COVID-19. Fout positieve testuitslagen kunnen leiden tot onnodige quarantaine en beperking van dagelijkse activiteiten en contacten.

Kosten, aanvaardbaarheid, haalbaarheid en implementatie(middelenbeslag)

Het missen van een COVID-19-diagnose brengt aanzienlijke kosten met zich mee. Voor een individu betekent dit dat ze mogelijk niet de ondersteunende zorg krijgen die ze nodig hebben en dat ze de ziekte kunnen verspreiden naar nauwe contacten. In een ziekenhuisomgeving plaatst een gemiste diagnose kwetsbare patiënten met een hoog risico op een mogelijk levensbedreigende ziekte. Vanuit een sociaal perspectief leidt een gemiste diagnose tot voortdurende verspreiding van ziekten in gemeenschappen met sociale, politieke en economische gevolgen.

Er zou een lagere drempel moeten zijn voor het testen van ouderen en psychogeriatrische patiënten bij ziekenhuispresentatie doordat ze zich vaker atypisch presenteren en een grotere kans hebben op een ernstig ziektebeloop en om aan de ziekte te overlijden. Dit geldt zeker voor de patiënten met cognitieve stoornissen omdat ze minder goed in staat zijn hun klachten aan te geven en voor patiënten die woonachtig zijn in verpleeghuizen of andere gedeelde woonvormen omdat er een hoger risico is op verspreiding van de ziekte onder (kwetsbare) medebewoners.

De kans op ziekte hangt o.a. af de actuele prevalentie van COVID-19. Op dit moment varieert de prevalentie sterk en is er nog veel onzekerheid over het verloop hiervan in de toekomst (seizoensvariatie en vaccinatiegraad).

Rationale van de aanbeveling

Er was geen tot een zeer lage bewijskracht van de voorspellende waarde van specifieke klinische symptomen voor de diagnose COVID-19. De meeste klinische symptomen zijn daarom niet opgenomen in deze aanbevelingen.

Desalniettemin wil de richtlijncommissie de meest voorkomende symptomen van COVID-19 en een aantal aspecifieke symptomen onder de aandacht brengen om de waarschijnlijkheid vóór de test en de daaropvolgende interpretatie van diagnostische testmodaliteiten te informeren.

Onderbouwing

Achtergrond

De diagnose van COVID-19 wordt bemoeilijkt door zowel geografische als temporele fluctuaties in de prevalentie van de ziekteachtergrond en het brede klinische spectrum van de ziekte. Zowel de achtergrondprevalentie als de klinische presentatie bepalen de voorafkans (pre-test probability) op ziekte en

daarmee de interpretatie van diagnostische modaliteiten en de achterafkans (post-test probability) van een COVID-19-diagnose. Tijdens perioden met een hoge COVID-19-achtergrondprevalentie zou de klinische verdenking hoger moeten zijn en neemt de waarschijnlijkheid van ziekte vóór de test (pre-test probability) toe.

COVID-19 heeft ook diverse klinische presentaties. Het klinische spectrum kan variëren van asymptomatische of presymptomatische infectie tot milde, matige, ernstige en kritieke ziekte. Om specifieke klinische symptomen als leidraad voor de diagnose te gebruiken, heeft het expertiseteam de voorspellende waarde van verschillende veelvoorkomende klinische symptomen bij de diagnose van COVID-19 beoordeeld. Deze omvatten verlies van smaak en geur, diarree, thoracale pijn en trombose. Veelvoorkomende symptomen passend bij COVID-19 zijn beschreven in Tabel 1.

Tabel 1. Symptomen passend bij COVID-19 *

Symptomen kunnen 2-14 dagen na blootstelling aan het virus optreden. Mensen met deze symptomen of een combinatie hiervan kunnen COVID-19 hebben.	Meest voorkomende symptomen • Hoesten • Benauwdheid • Verhoging of koorts Andere veelvoorkomende symptomen • Rillingen • Vermoeidheid • Spierpijn • Hoofdpijn • Keelpijn • Plotseling verlies van reuk en/of smaak (zonder neusverstopping) • Rhinorhoe • Misselijkheid of overgeven • diarree

* Gebaseerd op IDSA diagnostic guideline en de RIVM website.

Bij specifieke patiëntenpopulaties komen atypische presentaties van COVID-19 voor waarbij een COVID-19-diagnose dient te worden overwogen. In deze module wordt zowel de voorspellende waarde van specifieke symptomen bij volwassenen als bij specifieke patiëntenpopulaties, waaronder ouderen en kinderen, beschreven/bekeken. Het is belangrijk om aandacht te hebben voor de meest voorkomende klachten bij ouderen gezien hun frequente opname en het verhoogde risico op ernstig beloop van ziekte (Williamson, 2020).

Conclusies / Summary of Findings

very low GRADE	The sensitivity, specificity and positive predictive value for loss of smell and/or taste in the diagnosis of COVID-19 for patients presenting to hospital are uncertain. However, the loss of smell and/or taste, particularly without a blocked nose, has a high specificity – ranging from 0.89 to 0.99 and a positive predictive value of 63-91%. Sensitivity is low, ranging from 0.14 to 0.65. <i>Sources: Çalica, Utku 2020; Brendish, 2020; Payrony, 2020; Struyf, 2020</i>
very low GRADE	The sensitivity and the positive predictive value of the presence of diarrhea for the diagnosis of COVID-19 in patients who present themselves at the hospital are uncertain. The sensitivity ranged from 0.0 to 0.37. The positive predictive value of the presence of diarrhea ranged from 0.0 to 0.63 <i>Sources: Çalica Utku, 2020; Brendish, 2020; Payrony, 2020; Struyf, 2020</i>
no GRADE	No studies were identified in which the predictive value of thoracic pain or thrombosis for COVID-19 in adults were reported.
no GRADE	No studies were identified in which the predictive value of delirium, falls, decreased consciousness, hypothermia for COVID-19 in vulnerable and/or elderly patients were reported.

Samenvatting literatuur

Description of studies

Atypical symptoms at presentation in adults

Five studies (one systematic review and four clinical studies) reported on the predictive value of loss of smell and taste and diarrhea. One of the studies, a Cochrane review (Struyf 2020), searched for studies assessing the diagnostic accuracy of signs and symptoms for COVID-19 among patients presenting to primary care or hospital outpatient settings. The search was performed on the 27th of April 2020. The review included both cross-sectional and diagnostic case-control type studies. 16 Studies encompassing 7706 participants were included. In these studies, the prevalence of COVID-19 varied from 5% to 38%. Six studies were included that reported on the diagnostic accuracy of diarrhoea and one study reported on the diagnostic accuracy of loss of smell or loss of taste (see evidence table).

Brendish (2020) reported a clinical study in large UK hospital. The study population included adults (≥ 18 years old) presenting to the Emergency Department or Acute Medicine Unit with an acute respiratory illness or otherwise clinically suspected of having COVID-19. 1054 adults presenting to hospital with suspected COVID-19 were included, of whom 33.4% tested positive for COVID-19. A subset of 499 patients who received molecular

point-of-care testing (mPOCT) were asked detailed questions about their symptoms prior to the mPOCT result. The remaining patients were tested with RT-PCR. In this group only routinely collected data was used. The prevalence of COVID-19 was 39%.

Haehner (2020) reported the results of a cross-sectional study which included all patients presenting to a coronavirus testing center at a University Hospital in Germany. 500 patients were included and filled in a questionnaire which included questions on symptoms, time course, and an additional self-assessment of the patients' current smell, taste function, and nasal breathing compared to the level before the onset of symptoms. The percentage of patients who tested positive for COVID-19 was 6.8%.

Payrony (2020) reported the results of an observational study including 391 adult patients with suspected COVID-19 who were tested for SARS-CoV-2 at a university hospital. Symptoms were recorded by attending emergency physicians or resident physicians in a dedicated form detailing the patient's medical history. The prevalence COVID-19 in this study was 58%.

Çalica Utku (2020) described 297 patients who adhered to the case definition and who were admitted to a COVID-19 inpatient clinic. Patients were asked if they had fever, cough, sputum production, dyspnea, sore throat, myalgia, lumbago, weakness, rhinorrhea, headache, taste disorder, smell disorder, diarrhea, conjunctivitis and skin rash. In this study, the prevalence of COVID-19 was 48%.

Atypical symptoms at presentation in elderly patients

No studies were included in which the predictive value of delirium, falls, decreased consciousness, hypothermia for COVID-19 in elderly patients was reported.

Atypical symptoms at presentation in children

No studies were included in which the predictive value of symptoms matching Kawasaki disease or Guillain Barre for COVID-19 in children was reported.

Results

Diarrhea

In the Cochrane review (Struyf, 2020), six studies (1733 patients) were included that reported on the sensitivity and specificity of diarrhea as a symptom predictive for COVID-19. In these included studies, the sensitivity ranged from 0.0 to 0.15. The specificity ranged from 0.86 to 0.99. The results of these studies were not pooled in a meta-analysis, due to the small numbers of studies currently available, considerable heterogeneity across studies and the high risk of bias. The positive predictive values were not reported. We calculated that these values ranged from 0.0 to 0.43. However, two of these studies were small ($n=19$ / $n=29$) and in four of the studies the target population was COVID-19 pneumonia instead of COVID-19 disease. Brendish (2020) reported a sensitivity of 0.373 [95%CI 0.3 to 0.451] for the presence of diarrhea at presentation. The specificity was 0.824 [95%CI 0.771 to 0.867] and the positive predictive value 0.576 [95%CI 0.477 to 0.668]. Diarrhea was present in 99 patients at presentation (20%).

In the study by Çalica Utku (2020) the prevalence of diarrhea was 16% (49 of the 297 included patients). The sensitivity of this symptom for COVID-19 was 0.217 [95%CI 0.157 to 0.291], the specificity 0.883 [95%CI 0.823 to 0.925] and the positive predictive value 0.633 [95%CI 0.493 to 0.753].

Payrony (2020) reported on the diagnostic value of gastrointestinal complaints. Gastrointestinal symptoms, including such as vomiting, diarrhea, or abdominal pain, were present in 94 of the 391 included patients (24%). The percentages were comparable in COVID-19 positive and COVID-19 negative patients, resulting in

a sensitivity of 0.236 [95%CI 0.185 to 0.295], specificity of 0.753 [95%CI 0.682 to 0.812] and positive predictive value of 0.564 [95%CI 0.463 to 0.66].

Loss of smell or loss of taste

The Cochrane review included one study (870 participants) which reported on the sensitivity and specificity of loss of smell or loss of taste. In this study the sensitivity was 0.23 (95%CI 0.16 – 0.30) and the specificity 0.99 (95%CI 0.98 – 0.99). The positive predictive value is 0.795 [95%CI 0.655 to 0.888].

In the study by Brendish (2020), anosmia was present in 66 patients in a subgroup of 499 patients who were tested with mPOCT only (13%). The sensitivity of the presence of anosmia for COVID-19 was 0.331 [95%CI 0.259 to 0.412], the specificity 0.912 [95%CI 0.867 to 0.943] and the positive predictive value 0.712 [95%CI 0.594 to 0.807].

In the study by Haehner (2020), 69 patients (14%) presented with olfactory loss. For the sole symptom “smell loss”, the sensitivity was 0.647 [95%CI 0.479 to 0.785], the specificity 0.899 [95%CI 0.868 to 0.923] and the positive predictive value 0.319 [95%CI 0.221 to 0.436]. Excluding patients with a blocked nose increased the positive predictive value to 63% (specificity 97% sensitivity of 65%).

Thirty-four (8.7%) patients included in the study by Payrony (2020) reported anosmia. The sensitivity of anosmia for COVID-19 was 0.14 (95%CI 0.10–0.19), the specificity 0.98 (95%CI 0.95–1.00) and the positive predictive value 0.91 (95%CI 0.76–0.98).

Çalica Utku (2020) reported that a smell disorder was present in 50 patients (17%). The sensitivity of a smell disorder for the presence of COVID-19 was 0.231 [95%CI 0.169 to 0.306]. The specificity was 0.89 [95%CI 0.83 to 0.93] and the positive predictive value 0.66 [95%CI 0.522 to 0.776]. A taste disorder was present in 72 patients (24%). The sensitivity of this symptom was 0.357 [95%CI 0.283 to 0.438]. The positive predictive value 0.708 [95%CI 0.595 to 0.801]

Level of evidence of the literature

The level of evidence regarding the predictive value of symptoms was downgraded by 3 levels because of inconsistency (PPV range from no predictive value to moderate) and study limitations (risk of misclassification of symptoms and disease; unclear whether symptoms were measured independent from PCR test results).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

What is the predictive value of atypical symptoms for COVID-19 in adults, elderly, and children who presented at the hospital? More specifically,

- What is the predictive value of loss of smell, loss of taste, diarrhea, thoracic pain, or thrombosis for COVID-19 in adults who presented at the hospital?
- What is the predictive value of delirium, falls, decreased consciousness, hypothermia for COVID-19 in elderly who presented at the hospital?
- What is the predictive value of symptoms matching Kawasaki disease or Guillain Barre for COVID-19 in

children who presented at the hospital?

P1: adults who present themselves at the hospital with loss of smell, loss of taste, diarrhea, thoracic pain, or thrombosis

I: -

C: -

O: (positive) predictive value for COVID-19

P2: elderly patients who present themselves at the hospital with delirium, falls, decreased consciousness, hypothermia

I: -

C: -

O: (positive) predictive value for COVID-19

P3: Children who present themselves at the hospital with symptoms matching Kawasaki disease or Guillain Barre

I: -

C: -

O: (positive) predictive value for COVID-19

Relevant outcome measures

The guideline development group considered the positive predictive value as a critical outcome measure for decision making.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 14 October 2020. Three separate searches were performed: for adults, elderly patients, and children. The detailed search strategy is depicted under the tab Methods. The systematic literature searches resulted in 3342 hits (adults), 126 hits (elderly) and 110 hits (children). Studies were selected based on the following criteria clinical studies and/ or systematic reviews with a meta-analysis, reporting presenting data about the predictive value (diagnostic accuracy) of selected atypical symptoms for COVID-19 or data that can be used to calculate the predictive value.

Concerning adults, sixteen studies were initially selected based on title and abstract screening. After reading the full text, eleven studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies were included.

For the question concerning elderly patients, nine studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Concerning children, nine studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the tab Methods), and no studies were included.

Results

Five studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Aanvullende diagnostiek COVID-19 na negatieve PCR

Uitgangsvraag

Welke aanvullende diagnostiek is zinvol indien een patiënt negatief test voor SARS-CoV-2 en een aanhoudende verdenking op COVID-19 heeft?

De uitgangsvraag omvat de volgende deelvragen:

1. Wat is de meerwaarde van een herhaling van de PCR, inclusief dieper materiaal indien een patiënt negatief test voor SARS-CoV-2 en een aanhoudende verdenking op COVID-19 heeft?
2. Wat is de meerwaarde van serologie indien een patiënt negatief test voor SARS-CoV-2 en een aanhoudende verdenking op COVID-19 heeft?
3. Wat is de meerwaarde van beeldvorming indien een patiënt negatief test voor SARS-CoV-2 en een aanhoudende verdenking op COVID-19 heeft?

Aanbeveling

Herhaling PCR-test

Herhaal bij aanhoudende klinische verdenking de PCR, indien deze in eerste instantie negatief was. De PCR-test kan na 24 uur herhaald worden uit hetzelfde compartiment of meteen herhaald worden uit een dieper (sputum, BAL) compartiment of eventueel feces *

Verricht bij voorkeur een CT-thorax bij patiënten met een negatieve PCR, bij wie klachten minimaal 48 uur aanwezig zijn, er nog geen CT-scan is uitgevoerd en op basis van het klinisch beeld en de lokale prevalentie wel het vermoeden op COVID-19 bestaat. Indien beschikbaar, kan waar mogelijk en/of noodzakelijk gebruik gemaakt worden van echografie van de thorax.

Verricht de CT-thorax zonder IV-contrast (blanco) met dunne coupes en een voor de lokaal beschikbare CT-scanner geoptimaliseerd protocol.

Serologie

Overweeg serologie selectief te gebruiken om een diagnose te ondersteunen en interpreteer in combinatie met anamnese, vaccinatiestatus, immuunstatus, ziekte duur, kliniek, PCR-test en CT-scan.

Vaststellen of uitsluiten diagnose COVID-19

Hanteer onderstaande tabel en het stroomdiagram voor het vaststellen of uitsluiten van COVID-19 bij patiënten met een verdenking op COVID-19, een negatieve PCR-test en de uitkomsten van aanvullende diagnostiek.

Tabel 1. Interpretatie uitkomsten PCR-test en CT-thorax bij patiënten met verdenking op COVID-19

1 ^e PCR	CT-thorax*	Alternatieve diagnose	2 ^e PCR**	Conclusie
positief		Niet nodig	Niet nodig	COVID-19 aangetoond
negatief	CO-RADS 1	ja/nee	Niet nodig	Geen aanwijzingen voor COVID-19
negatief	CO-RADS 2-3	ja	Niet nodig	Geen aanwijzingen voor COVID-19
negatief	CO-RADS 2-3	nee	Indien negatief	Geen aanwijzingen voor COVID-19
negatief	CO-RADS 2-3	nee	Indien positief	COVID-19 aangetoond
negatief	CO-RADS 4-5	ja	Indien negatief***	Geen aanwijzingen voor COVID-19
negatief	CO-RADS 4-5	ja	Indien positief***	COVID-19 aangetoond
negatief	CO-RADS 4-5	nee	Indien negatief	MDO voor definitieve interpretatie
negatief	CO-RADS 4-5	nee	Indien positief	COVID-19 aangetoond

* CT-thorax is pas een goede voorspeller bij (pulmonale) klachten > 2 dagen.

**De PCR kan na 24 uur herhaald worden uit hetzelfde compartiment of meteen herhaald worden uit een dieper (sputum, BAL) compartiment of eventueel feces.

***Als er een *bewezen* alternatieve diagnose is die ook verklarend is voor CO-RADS 4-5, kan een 2^e PCR achterwege blijven

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Herhaling PCR

De SARS-CoV-2 PCR-test wordt gezien als de gouden standaard voor het stellen van de diagnose van een SARS-CoV-2 infectie. Een negatieve PCR-test uitslag, echter, sluit niet in alle gevallen een SARS-CoV-2 infectie uit. Vanwege de variabiliteit in virale lading gedurende de ziekte episode zal hierbij o.a. de timing van afname, afname materiaal, de achtergrondprevalentie en/of mutaties in het virus een rol spelen. Bij hoge klinische verdenking op een SARS-CoV-2 infectie zal daarom na een eerste negatieve PCR-test uitslag nog vervolgdagnostiek worden ingezet om de klinische verdenking te bevestigen danwel te verwerpen.

Uit de literatuuranalyse van de cruciale uitkomstmaat additionele diagnose COVID-19 komt naar voren dat herhaling van de SARS-CoV-2 PCR-test bij patiënten die een eerste keer negatief testen en wel klinisch verdacht zijn voor een COVID-19 infectie slechts een beperkt percentage additionele diagnoses oplevert, namelijk tussen de 2 en 4% (Challener, 2020; Green 2020; Lepak, 2020). Bij patiënten waar de voorafkans op basis van CT-scan of ernst van de klachten redelijk tot hoog was leverde herhaald testen m.b.v. PCR-test 12,5 tot 29,4% additionele diagnoses op. (Giannito, 2020; Li, 2020).

Voor de meerwaarde van het gebruik van dieper materiaal op de uitkomstmaat additionele diagnose COVID-19 is tot nu toe beperkt bewijs gevonden middels deze literatuuranalyse. Enkel in de studie van Giannitto et al. wordt in de meerderheid van de gevallen (73,5%) de tweede PCR-test op dieper materiaal (BAL) uitgevoerd. In deze studie wordt bij 29,4% van de patiënten een additionele diagnose COVID-19 gesteld m.b.v. de tweede PCR test, echter dit betreft in totaal maar een klein aantal patiënten (n=68). Het expertiseteam is van mening dat afname van dieper materiaal (sputum, BAL) of eventueel feces na een eerste negatieve PCR-test wel meerwaarde heeft in de klinische praktijk.

De bewijskracht van de diagnostische waarde van de herhaal PCR-test werd als laag tot zeer laag

beoordeeld. Er werd geoordeeld door de werkgroep dat de aanwezige beperkingen in onderzoeksopzet, veelal retrospectief, wisselende opzet en inclusie-criteria per studie, patiënten-selectiebias, de inconsistentie in studieresultaten en het geringe aantal patiënten invloed hebben op de uiteindelijke zekerheid van bovenstaande resultaten.

Uit deze resultaten kan geconcludeerd worden dat middels een tweede PCR afname er additionele diagnoses COVID-19 kunnen worden gesteld en dat dit met name relevant kan zijn bij patiënten met aanvullende bevindingen die de verdenking van COVID-19 kunnen ondersteunen, zoals afwijkingen op CT-scan of klinische kenmerken.

Antigeensneltest

Er zijn ook antigeensneltesten beschikbaar. Gezien er accuratere testen inzetbaar zijn, is hier verder geen uitgebreide literatuursearch naar verricht. Daarom worden antigeentesten alleen kort besproken in de Overwegingen. Antigeensneltesten zijn immunoassays die de aanwezigheid van een specifiek viraal antigeen detecteren, wat een huidige virale infectie impliceert. Deze testen worden uitgevoerd met een naso-/keeluitstrijk die rechtstreeks in de extractiebuffer of het reagens van het assay worden geplaatst. Antigeentesten zijn relatief goedkoop en snel, de resultaten van de test zijn na ongeveer 15 minuten beschikbaar. Echter, sneltesten vereisen voldoende getraind personeel om ze effectief te kunnen uitvoeren en dienen handmatig per stuk en dus niet in bulk ingezet te worden waardoor ze arbeidsintensiever dan PCR-tests kunnen zijn.

De specificiteit van antigeensneltesten is over het algemeen net zo hoog als PCR. Antigeensneltesten voor SARS-CoV-2 zijn over het algemeen minder sensitief dan PCR-gebaseerde testen. Een Cochrane systematische review van 22 studies van antigeensneltesten wees uit dat de sensitiviteit aanzienlijk varieerde per test (0-99%) met een gemiddelde sensitiviteit van 56,2% (Dinnes, Cochrane, augustus 2020). Studies suggereren dat antigeensneltesten het beste presteren wanneer de persoon wordt getest in een vroeg stadium van infectie met SARS-CoV-2, wanneer de virale load over het algemeen het hoogst is (Dinnes, 2020). De sensitiviteit van antigeensneltesten in de ziekenhuisomgeving is momenteel onvoldoende onderzocht, maar is waarschijnlijk aanzienlijk lager dan van RT-PCR. Een lagere sensitiviteit van de antigeensneltesten kan resulteren in fout-negatieve testuitslagen en gemiste COVID-19 diagnoses in de ziekenhuisomgeving. Het expertiseteam ziet op dit moment geen plaats voor het gebruik van antigeensneltesten bij het stellen van de diagnose COVID-19 bij patiënten die in het ziekenhuis worden gezien of opgenomen, omdat het belangrijk is om een gemiste diagnose te voorkomen in de ziekenhuisomgeving (d.w.z. fout-negatieven).

Serologie

Het is mogelijk serologie te bepalen om na te gaan of iemand COVID-19 heeft of heeft doorgemaakt. Er wordt veel gebruik gemaakt van zogenaamde Ig Totaal testen waarmee de aanwezigheid van SARS-CoV-2 specifiek IgM, IgA en IgG gemeten wordt, zonder daarbij te differentiëren tussen het type antistof (Taskforce serologie 2020; Lassaunière, 2020). Deze testen zijn zeer gevoelig en maken het mogelijk om vanaf ziektedag 4-7 antistofrespons op de infectie aan te tonen. De sensitiviteit is ongeveer 75% vanaf dag 7 bij patiënten met een ernstige infectie en loopt op naar 98% bij dag 10 en 99% vanaf dag 14. De specificiteit is 99,4% (n=1067) in klinische en niet klinische patiënten in vergelijking met PCR. Seroprevalentie is landelijk aan het stijgen door een groeiende populatie met doorgemaakte infectie en een groeiende vaccinatiegraad. Dit bemoeilijkt

de interpretatie van de serologie voor diagnose van COVID-19 bij een negatieve PCR. Voor interpretatie van serologie is het van belang om een goede anamnese af te nemen om te beoordelen of een patiënt reeds COVID-19 heeft doorgemaakt of vaccinatie heeft gehad.

Beeldvorming

Er is onvoldoende bewijs over de meerwaarde van het gebruik van beeldvorming bij patiënten die negatief testen voor SARS-CoV-2. Er is slechts één studie hierover geïnccludeerd. Echter, het expertiseteam is van mening dat beeldvorming bij patiënten die worden opgenomen met (klinische verdenking op) COVID-19 en een negatieve PCR-test wel meerwaarde heeft in de klinische praktijk. In de praktijk wordt de CT-scan bij negatieve PCR-test gebruikt voor ondersteuning van de diagnose COVID-19. Daarnaast is de ervaring in de praktijk dat bij hoge klinische verdenking op COVID-19 en negatieve PCR, na de CT-scan de diagnose regelmatig verschuift naar andere klinische verwekker of alternatieve diagnose (bronchiolitis/ bronchopneumonie/ decompensatio cordis) waardoor verdenking op COVID-19 wordt losgelaten en patiënt uit isolatie kan.

Aan het begin van het diagnostisch traject kan een X-thorax worden overwogen, maar deze heeft een lagere sensitiviteit en specificiteit dan een CT-thorax (Fleischner, 2020). De diagnostische waarde van een CT-scan van de longen bij het stellen van de diagnose COVID-19 lijkt beter in een populatie met een hoge prevalentie van COVID-19, zoals COVID-verdachte patiënten met een opname indicatie (Fleischner, 2020; Ai, 2020; Fang, 2020; Long, 2020). De CT-scan kan direct ook een indicatie geven van de ernst van de ziekte.

Naast CT-scan en X-thorax is beeldvorming van de longen bij patiënten met (verdenking op) COVID-19 mogelijk met echografie. Dit valt onder zgn. target of point of care echografie (POCUS) en kan worden ingezet als verlengstuk van het lichamelijk onderzoek. Het expertiseteam is van mening dat er geen vastomlijnde plaatsbepaling voor de echografie mogelijk is, gezien de lage specificiteit waardoor accuratesse en toepasbaarheid van echografie van de longen afhankelijk is van de prevalentie van de ziekte, alsook de ervaring van de echografist. De waarde voor de patiënt hangt daarnaast dus sterk af van de lokale situatie (o.a. beschikbaarheid dan wel afwezigheid van PCR voor primaire diagnostiek en ook aanwezigheid van echografie apparatuur, alsook de alternatieve imaging als CT en röntgenapparatuur). Bovendien is het expertiseteam van mening dat CT, vergeleken met longechografie, specifiekere en meer mogelijkheden biedt om centrale pulmonale en cardiovasculaire veranderingen bij COVID-19 of eventuele alternatieve diagnoses aan te tonen. Mogelijk dat kosteneffectiviteit studies naar toepassing van longechografie in de nabije toekomst de waarde van deze modaliteit in de praktijk kan vaststellen.

Het is van belang te realiseren dat het mogelijk is dat een CT-scan, X-thorax of target echo bij vroege (<48 uur) en/of milde ziekte geen afwijkingen toont, omdat er zich nog geen pulmonale manifestaties hebben ontwikkeld (Bernheim, 2020), of als het patiënten met COVID-19 betreft zonder longbetrokkenheid. Daarom is de CT-scan, X-thorax of target echo altijd een aanvulling op en geen alternatief voor NP SARS-CoV-2 PCR-tests en serologie. Voor het protocol voor CT-thorax verwijst het expertiseteam naar het Standpunt COVID-19 CT-thorax protocol (NVKF).

Ten slotte hangen de negatieve en positieve voorspellende waarde van zowel de CT, echografie, serologie als PCR-test sterk af van de achtergrondprevalentie van COVID-19 in de populatie.

Daarbij zijn verschillen door de tijd en regionale verschillen mogelijk.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Diagnostiek na eerste negatieve PCR-test kan voor patiënten ongemakkelijk zijn (nasofaryngeaal swab,

bloedafname). Fout-positieve testuitslagen kunnen leiden tot onnodige quarantaine en beperking van dagelijkse activiteiten en contacten waar aan de andere kant aanvullende diagnostiek ook zou kunnen leiden dat de patiënt uit de isolatie kan.

Kosten (middelenbeslag), haalbaarheid en implementatie

De CT-thorax is duurder dan de X-thorax, maar heeft de voorkeur in verband met een betere diagnostische accuratesse (zie hierboven). De kosten van het uitvoeren van een PCR-test ligt beduidend lager dan van een CT-thorax een (doorgaans minder dan 50 euro).

Beschikbaarheid van apparatuur (CT-scan en röntgenapparatuur) is relevant in perioden dat de prevalentie van het aantal mensen met een COVID-19 infectie in de samenleving heel hoog is. Het gaat hierbij niet alleen/ zozeer om de capaciteit van de CT scan en röntgenapparatuur, maar vooral om de beschikbaarheid van personeel (radiodiagnostisch laboranten).

Onderbouwing

Achtergrond

Voor het stellen van de diagnose COVID-19 wordt de RT-PCR-test als gouden standaard gehanteerd. Een deel van de patiënten zal echter een fout-negatieve testuitslag krijgen. Fout-negatief verwijst hierbij naar iemand die de ziekte echt heeft, maar bij wie de uitslag van de PCR-test negatief is. De sensitiviteit van RT-PCR-test bij gebruik van nasofaryngeaal materiaal (NP) wordt beïnvloed door diverse factoren gerelateerd aan de uitvoer van de test en klinische factoren (Arevalo-Rodriguez, 2020; Chan, 2020; Li, 2020; Patel, 2020; Vankrunkelsven, 2020; Vogels, 2020). De sensitiviteit van de NP-PCR-test hangt ook af van het moment van testen in het stadium van de ziekte en is waarschijnlijk hoger in het begin van het ziekteproces en lager in een later ziektestadium in verband met mate van uitscheiding van virus in de nasofarynx (Wölfel, 2020; Liu 2020). De vraag is welke aanvullende diagnostiek zinvol is om in te zetten bij patiënten met een negatieve testuitslag maar wel een verdenking op COVID-19.

Conclusies / Summary of Findings

Second PCR

Very low GRADE	A second PCR test in patients with symptoms that are consistent with a COVID-19 infection and an initial negative PCR test result yielded a low number of additional COVID-19 diagnoses (2-4%). A second PCR test in patients <u>who were reported to have a moderate to high pre-test probability of COVID-19 (based on symptom severity or a CT scan)</u> and an initial negative PCR test yielded 12.5% to 29.4% additional diagnoses of COVID-19. Although a second negative PCR test result may not completely rule out COVID-19 in this population, the negative test result can help inform use of further diagnostic testing and help direct inform clinical therapy. There is very little evidence from which to draw conclusions about the value of specimens from the lower respiratory system; the use of these specimens seemed to result in more additional diagnoses but patient numbers were very low and the results are likely to be affected by selection bias. <i>Sources: Challener, 2020; Giannitto, 2020; Green, 2020; Lepak, 2020; Li, 2020</i>

Serology

Very low GRADE	The use of serology (IgG and IgM) in patients with symptoms consistent with a COVID-19 infection, who had a high pre-test probability of COVID-19, a negative initial PCR test result yielded a high percentage of additional diagnoses (88.5% and 93.1%). The added value of serological testing may be limited, as a negative result in this population will not completely rule-out a COVID-19 infection. There is a lack of evidence to assess the value of serological testing in a population with a low pre-test probability of COVID-19 infection. <i>Sources: Guo, 2020; Pérez-García, 2020</i>

Imaging

Very low GRADE	There is insufficient evidence to assess the value of imaging in patients with symptoms of suspected COVID-19 infection and a negative PCR test result. <i>Sources: Giannitto, 2020</i>

Samenvatting literatuur

Description of studies

Second PCR

Challener (2020) performed a retrospective study among both inpatients and outpatients at a university hospital who underwent PCR testing for COVID-19 between 10 March and 13 April 2020. Testing took place across four campuses in the United States (Minnesota, Arizona, Florida, and Wisconsin). This study included all patients who received serial PCR testing for suspected COVID-19, and specifically investigated patients with multiple tests after the first test results were negative. The study also performed a subgroup analysis for repeat tests that were performed within seven days of the first test, to reduce error from patients who may have become infected between the first and second tests. Most specimens came from upper respiratory tract

swabs (ie, oropharynx, nasopharynx, or both). The study population consisted of 1113 patients who underwent repeat testing within seven days, 575 (25.4%) were inpatients and 1687 (74.6%) were outpatients. Median age was 48 years (IQR 35-61 years) and 39.6% of the population were men.

Giannitto (2020) performed a retrospective study using a database including consecutive patients admitted to the Emergency Department of an academic hospital in Milan (Italy) between 1 and 29 March 2020. This study included patients with a moderate or high pretest probability of COVID-19 infection, with an initial negative PCR test. Out of 87 patients who underwent a repeat PCR test, data were available for 68 patients. For the first PCR test specimens from the nasopharynx were used. For the repeat test, the preferred choice was a specimen from bronchoalveolar lavage (BAL) (73.5% BAL; 8.9% BAL and nasopharynx, 17.6% nasopharynx). All 68 patients presented with fever (temperature > 37.5°C), cough and dyspnoea. Median age was 62.5 years (SD 1.8, range 26-87 years), and 60.3% were men.

Green (2020) conducted a retrospective study using a large data set including patients who were tested at multiple hospital locations in the New York City area between 10 March and 1 May 2020. This included outpatients, admitted patients and patients visiting the Emergency Department. A total of 3,432 patients underwent repeat PCR testing. For the initial PCR test, 241 patients got an invalid result, in 2280 patients COVID-19 was not detected, and in 114 patients the test result was indeterminate. Specimens for the PCR test were obtained from the nasopharynx (initially also the oropharynx). One of the aims of this study was to investigate the value of repeat tests on the same day. No demographic characteristics were available for the subgroup of patients with an initial negative, invalid or indeterminate PCR test result.

Lepak (2020) conducted a retrospective study in a tertiary care academic centre, in a low-prevalence setting in the United States (Wisconsin). The study population consisted of 660 patients who underwent multiple PCR tests between 12 March and 5 May 2020. The initial PCR test was negative in 638 patients, and 275 of these patients were symptomatic. Tests were conducted in both inpatients (n=63) and outpatients (n=212). Inpatients were tested in case of symptoms consistent with possible COVID-19 (e.g. unexplained fever, chills, cough, shortness of breath/hypoxia, loss of smell or taste, fatigue, vomiting or diarrhoea, and/or sore throat). Most repeat tests for inpatients met clinical suspicion for high-risk or high likelihood of the patient actually having COVID-19. Outpatients were initially only tested in case of moderate or severe symptoms, but over time testing was also available to persons with high-risk conditions and symptoms compatible with COVID-19. PCR tests were performed on specimens from the nasopharynx. A total of 275 symptomatic patients (257 adults, 18 children) underwent at least one repeat PCR test. No demographic characteristics were available for this subgroup of 275 patients.

Li (2020) conducted a retrospective study in a hospital designated for the treatment of patients with COVID-19 in Wuhan (China). The study included 610 hospitalized patients clinically diagnosed with COVID-19 based on a CT scan demonstrating viral pneumonia between 2 February and 17 February 2020. Confirmed COVID-19 was defined as a positive PCR result. For patients with an initial negative, dubious positive or weakly positive PCR test result, a repeat test was performed after one or two days. PCR tests were performed on pharyngeal specimens. There were 384 patients with a first negative PCR test, 57 with a dubious positive test and 1 with a weakly positive test. No demographic characteristics were available for these subgroups.

Long (2020) conducted a retrospective study in two academic hospitals in the United States (University of Washington in Seattle, Washington and Stanford University in Stanford, California). The study involved both symptomatic and asymptomatic adult patients who underwent a PCR test between 2 March and 7 April 2020. Symptomatic patients were tested if they exhibited one or more new symptoms of acute respiratory infection, combined with pertinent risk factors, or based on clinical judgement. PCR tests were performed on specimens

from the nasopharynx. For the University of Washington, a subgroup analysis was reported for a group of 302 symptomatic patients who were retested within seven days of an initial negative PCR test. No demographic characteristics were available for this subgroup of 302 patients.

Serology

Guo (2020) conducted a prospective cohort study, including two cohorts. One of these cohorts consisted of 101 inpatients at hospitals in Wuhan (China) in January 2020. Paired throat swab and blood samples were taken from each patient, 1-39 days after disease onset. Out of these patients, 58 cases (5 severe and 53 mild to moderate) were suspected to be infected based on clinical manifestations, CT scans, and epidemiology but the results of a first test using metagenomic sequencing or PCR test were negative. In this cohort the diagnostic value of IgM was investigated. No demographic characteristics were available for this subgroup of 58 patients.

Pérez-García (2020) conducted a prospective study in an academic hospital in Madrid (Spain). The study population consisted of 61 patients who were admitted for at least five days between 9 February and 2 April 2020. These patients had a clinical and radiological diagnosis of pneumonia of unknown aetiology and a negative initial PCR test result. Serum samples were tested to detect IgG and IgM antibodies. Median age was 67 years (range 57 to 73 years) and 73.8% were men. Median duration since onset of symptoms was 17 days (IQR 15 to 20 days).

Imaging

The retrospective study by **Giannitto (2020)** was based on a database including consecutive patients admitted to the Emergency Department of an academic hospital in Milan (Italy) between 1 and 29 March 2020. This study included patients with a moderate or high pre-test probability of COVID-19 infection, with an initial negative PCR test. Out of 87 patients who underwent a repeat PCR test, data were available for 68 patients. For the PCR test specimens from the nasopharynx were used. A group of 68 patients underwent a CT scan within four days of the initial negative PCR test. All of these patients presented with fever (temperature > 37.5°C), cough and dyspnoea. Median age was 62.5 years (SD 1.8, range 26-87 years), and 60.3% were men.

Results

Second PCR

Challener (2020) showed that repeating the PCR test within seven days of the initial negative PCR test yielded 22 additional diagnoses in 1113 patients (2%). The median interval between the initial negative test and the positive test was four days (IQR 3 to 9 days).

The study of **Giannitto (2020)** showed that 20 out of 68 patients (29.4%) received a positive test result from the repeat PCR, mostly using specimens from the lower respiratory system (73.5% BAL). Subgroup analysis per type of specimen showed that in patients where a nasopharyngeal specimen was used 1/12 (8.3%) patients received a positive result, while 15/50 (30%) patients who underwent BAL PCR received a positive result, and 4/6 (67%) of patients who underwent repeated nasopharyngeal and BAL PCR received a positive result.

The study of **Green (2020)** showed that 45/241 patients (18.7%) with an initial invalid PCR test result tested positive on the same day. Among 2280 patients where the disease was not detected initially, 49 patients (2.1%) got a positive test result on the same day. Among 114 patients with an initial indeterminate test result,

16 (14.0%) got a positive test result on the same day.

Lepak (2020) investigated the number of additional diagnoses in both inpatients and outpatients. In the group of 63 symptomatic inpatients, the repeat PCR test did not yield any additional diagnoses of COVID-19. The median duration to repeat testing was four days (range 0 to 26 days). In the group of 212 outpatients, six patients with an initial negative test had a positive repeat test result (2.8%). In four of these patients, the interval between the initial negative test and repeat positive test was more than ten days. The median time to repeat testing was 13 days (5-17).

In the study of **Li (2020)** the first repeat PCR test among 384 patients with an initial negative PCR test yielded 48 additional positive tests (12.5%). In addition, the repeat PCR test showed a dubious positive test result in 27 patients (7%).

Serology

The study of **Guo (2020)** showed that 54 out of 58 'probable cases' (93.1%) had a positive test result for IgM. The study of **Pérez-García (2020)** showed that in 54 out of 61 patients (88.5%) antibodies against COVID-19 were detected; 88.5% were positive for IgG antibodies and 23 patients (37.7%) were also positive for IgM antibodies.

Imaging

Out of the 68 patients with a moderate or high pretest probability of COVID-19 infection, the CT scan showed features suggestive of COVID-19 in 24 patients (35.3%). Out of these 24 patients, 14 patients (58.3%) had a positive second PCR test result and 10 patients (41.7%) had a negative second PCR test result. Using the second PCR test as the gold standard, CT scans resulted in 14 additional diagnoses. The median duration from onset of symptoms was 7 days (SE 0.20 days, range 1-22 days).

Level of evidence of the literature

Second PCR

The level of evidence regarding the outcome measure 'additional COVID-19 diagnoses' started at 'high', but was downgraded by three levels because of study limitations (-1; risk of bias), conflicting results (-1; inconsistency), and applicability (-1; bias due to indirectness).

Serology

The level of evidence regarding the outcome measure 'additional COVID-19 diagnoses' started at 'high', but was downgraded by three levels because of study limitations (-1; risk of bias) and the low number of included patients (-2; imprecision).

Imaging

The level of evidence regarding the outcome measure 'additional COVID-19 diagnoses' started at 'high', but was downgraded by three levels because of study limitations (-1; risk of bias) and the low number of included patients (-2; imprecision).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

P: patients with symptoms of suspected COVID-19 infection and a negative PCR test result
 I: second PCR (including different samples)
 C: no additional test
 O: additional COVID-19 diagnosis

P: patients with symptoms of suspected COVID-19 infection and a negative PCR test result
 I: serology
 Gold standard: PCR
 O: additional COVID-19 diagnosis

P: patients with symptoms of suspected COVID-19 infection and a negative PCR test result
 I: imaging
 Gold standard: PCR
 O: additional COVID-19 diagnosis

Relevant outcome measures

The working group considered the number of additional COVID-19 diagnoses as a critical outcome measure for decision making. This outcome measure is defined as the number of additional diagnoses in the group of patients that underwent additional diagnostic testing using a second PCR test, serology and/or imaging.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 29 September 2020.

The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1170 hits. Studies were selected based on the following criteria:

- inpatient or outpatient adult patients with symptoms of suspected COVID-19 infection;
- patients with a first negative PCR test, who underwent additional diagnostic tests involving a second PCR test, serology and/or imaging;
- a sample size of at least 50 patients.

136 studies were initially selected based on title and abstract screening. After reading the full text, 128 studies were excluded and eight studies were included.

Results

Eight studies were included in the analysis of the literature. Six studies have investigated the value of a second PCR, two studies have investigated the value of serology, and one study that investigated the value of a second PCR test also investigated the value of imaging. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 04-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Serologie na vaccinatie of herinfectie met COVID-19

Uitgangsvraag

Wat is de waarde van serologie, in het bijzonder het verloop van de serodynamiek van IgG antistoffen tegen SARS-CoV-2, om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn?

Aanbeveling

Gebruik indien nodig de voor het ziekenhuis beschikbare serologische mogelijkheden bij patiënten met verdenking op COVID-19 die gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad. Vooralsnog kan geen advies gegeven worden of en wanneer serologie in te zetten, gezien het ontbreken van wetenschappelijk bewijs.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Vooralsnog zijn er geen studies gepubliceerd die antwoord kunnen geven op de vraag wat de waarde is van serologie om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn. Eén studie werd geïncorporeerd in de literatuuranalyse (Bergwerk, 2021). In deze studie werd postinfectie N-specifieke IgG antistoffen onderzocht bij volledig gevaccineerde gezondheidsmedewerkers met een doorbraakinfectie. Echter, de afkapwaarde voor een positieve testuitslag werd niet beschreven en de veranderingen in IgG levels werden niet gerapporteerd.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Niet van toepassing.

Kosten (middelenbeslag)

Vanwege het ontbreken van evidence voor de gunstige effecten van serologische assays bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad, zijn de kosten geen overweging.

Aanvaardbaarheid, haalbaarheid en implementatie

Ziekenhuizen verschillen in de beschikbaarheid en het gebruik van serologische assays bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad. Het is mogelijk dat lokaal gebruik wordt gemaakt van kwantitatieve en semi-kwantitatieve serologische assays die het mogelijk maken serodynamiek te vervolgen en daar conclusies aan te verbinden met betrekken tot het optreden van doorbraakinfecties ondanks vaccinatie of herinfecties.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Vooralsnog zijn er geen studies gepubliceerd die antwoord kunnen geven op de vraag wat de waarde is van serologie om de diagnose COVID-19 te stellen bij patiënten die eerder een COVID-19 infectie hebben gehad of gevaccineerd zijn.

Ziekenhuizen verschillen in de beschikbaarheid en het gebruik van serologische assays. Het is mogelijk dat

lokaal gebruik wordt gemaakt van kwantitatieve en semi-kwantitatieve serologische assays die het mogelijk maken serodynamiek te vervolgen en daar conclusies aan te verbinden met betrekken tot het optreden van doorbraakinfecties ondanks vaccinatie of herinfecties.

Onderbouwing

Achtergrond

Voor het stellen van de diagnose COVID-19 wordt de RT-PCR-test als gouden standaard gehanteerd. Een deel van de patiënten zal echter een fout-negatieve testuitslag krijgen, omdat ze zich te laat presenteren en SARS-CoV-2 RNA al niet meer detecteerbaar is in de bovenste luchtwegen. In de module "Aanvullende diagnostiek COVID-19 na negatieve PCR" staat beschreven wat de rol is van serologie en beeldvorming bij patiënten met een verdenking op COVID-19 maar een negatieve PCR-test. Deze aanbevelingen hebben betrekking op patiënten die niet eerder een infectie hebben doorgemaakt. Inmiddels ziet men in het ziekenhuis steeds vaker patiënten die zich melden met een mogelijke herinfectie. Daarnaast zijn er patiënten die een vaccinatie voor COVID-19 hebben ontvangen, maar wel klachten hebben die passen bij COVID-19. De vraag is of de serodynamiek van IgG antistoffen tegen SARS-CoV-2 gebruikt kan worden om de diagnose COVID-19 te stellen als aanvulling op de PCR-test (add-on) bij patiënten met klachten die passen bij COVID-19 maar gevaccineerd zijn of eerder een COVID-19 infectie hebben gehad.

Conclusies / Summary of Findings

No GRADE	No evidence was found regarding the diagnostic accuracy of serology in patients with suspected COVID-19 who either have had a previous COVID-19 infection or have been fully vaccinated against SARS-CoV-2 <i>Sources: -</i>

Samenvatting literatuur

Description of studies

Vaccinated population with suspected COVID-19

Bergwerk (2021) performed a prospective cohort study in one Medical Center in Israel to assess the effectiveness of the BNT16b2 vaccine among health care workers and to examine possible correlates of protection and infectivity in this population. A breakthrough infection was defined as the detection of SARS-CoV-2 using RT-PCR in patients with 11 or more days after receipt of a second dose of BNT162b2. From the cohort of 11,453 fully vaccinated health care workers, 1497 (13.1%) underwent RT-PCR testing during the study period, within which 39 breakthrough cases (2.6%) were detected. Data regarding post-infection N-specific IgG antibodies were available for 22 of these 39 case patients (56%) on days 8 to 72 after the first positive result on RT-PCR assay.

Population with suspected COVID-19 with previous COVID-19 infection

No studies were included investigating patients with suspected COVID-19 who had a previous COVID-19 infection.

Results

Vaccinated population with suspected COVID-19

1. Diagnostic accuracy

Bergwerk (2021) included 22 cases with vaccine breakthrough infection in the analysis. Four of these cases (18%) did not have an immune response, as detected by negative results on N-specific IgG antibody testing. Two of these workers were asymptomatic (Ct values, 32 and 35), one underwent serologic testing only on day 10 after diagnosis, and one had underlying immunosuppression. It was not reported whether the results for IgG antibody testing were positive or negative for the matched controls. Unfortunately, neither the threshold for positivity of N-specific IgG antibody testing or the changes in IgG levels were reported in the article. Therefore, the sensitivity of significant changes of IgG levels against SARS-CoV-2 to diagnose recent COVID-19 in patients with clinical suspicion of COVID-19 who have been vaccinated could not be evaluated.

Population with suspected COVID-19 with previous COVID-19 infection

1. Diagnostic accuracy

No studies were included investigating patients with suspected COVID-19 who have had a previous COVID-19 infection.

Level of evidence of the literature

The level of evidence of the outcome diagnostic accuracy was not assessed due to lack of studies.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the sensitivity of significant changes of IgG levels against SARS-CoV-2 to diagnose recent COVID-19 in patients with clinical suspicion of COVID-19 and who have had a previous COVID-19 infection or have been vaccinated?

P: Patients with suspected COVID-19 who either have had a previous COVID-19 infection or have been fully vaccinated against SARS-CoV-2

I: IgG antibodies to SARS-CoV-2, with sequential measurements, performed within a maximum of 6 weeks from symptom onset

C: none

R: molecular test, RT-PCR, antigen test, histology, CT-scan

O: diagnostic accuracy: sensitivity, specificity

Relevant outcome measures

The guideline development group considered both sensitivity and specificity as a critical outcome measure for decision making. A priori, the working group did not define the outcome measures listed above but used the definitions used in the studies.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 14th October 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 173 hits. Studies were selected based on the following criteria: clinical studies and/ or systematic reviews with a meta-analysis, presenting data about the diagnostic accuracy of serology in

populations that fitted the PICO. A total of thirteen studies were selected based on title and abstract screening. After reading the full text, twelve studies were excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

Results

One study was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The risk of bias could not be assessed.

Verantwoording

Laatst beoordeeld : 01-02-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Referenties

Bergwerk, M., Gonen, T., Lustig, Y., Amit, S., Lipsitch, M., Cohen, C.,... & Regev-Yochay, G. (2021). Covid-19 breakthrough infections in vaccinated health care workers. New England Journal of Medicine.

Preoperatieve screening naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie

Uitgangsvraag

Op welke manier dienen patiënten die een operatie onder algehele anesthesie ondergaan te worden gescreend op aanwezigheid/afwezigheid van infectie met SARS-CoV-2?

Clinical question

How should patients who undergo surgery under general anesthesia be screened for SARS-CoV-2 infection?

This clinical question encompasses the following underlying questions:

1. What are reasons to perform pre-operative screening for SARS-CoV-2? And do these reasons differ for certain patient populations?
2. What precautions should one undertake if no screening is possible? And are these precautions different for elective, semi-elective and urgent surgery?
3. What measures should be taken if a patient has symptoms or a positive screening outcome pre-operatively? And are these measures different for elective, semi-elective and urgent surgery?

Aanbeveling

Verricht bij alle patiënten boven de 18 jaar een zorgvuldige en grondige anamnese gericht op mogelijke COVID-klachten van de patiënten en zijn/haar omgeving. Benadruk het belang voor zowel de patiënt als de zorgverlener van deze anamnese en consequenties indien klachten onverhoopt niet (h)erkent worden. Zie de bijlage 'Vragen bij screening op COVID-19' als voorbeeld voor de anamnese. Patiënten met klachten vallen buiten de richtlijnmodule.

Indien sprake is van risiconiveau 1 (waakzaam):

Verricht geen aanvullende screening met PCR indien de anamnese negatief is.

Indien sprake is van risiconiveau 2, 3, 4 of 5 (zorgelijk, ernstig, zeer ernstig en lockdown):

Overweeg bij patiënten van 65 jaar en ouder die niet volledig zijn gevaccineerd (**volledige vaccinatie houdt in: inclusief booster**) preoperatief onderzoek naar de mogelijke aanwezigheid van een SARS-CoV-2 infectie te verrichten door een diepe nasofaryngeale PCR.

Zie het stroomschema.

Aanbevelingen met betrekking tot screenen middels PCR en de urgentie van de operatie

Semi-acute en acute patiënten

Overweeg om patiënten van 65 jaar en ouder die niet volledig zijn gevaccineerd (**volledige vaccinatie houdt in: inclusief booster**) zijn bij risiconiveau 2, 3, 4 en 5 te testen door onmiddellijk een nasofaryngeale PCR test uit te voeren wanneer een chirurgische ingreep waarschijnlijk is, zelfs indien deze nog niet definitief vaststaat (bijvoorbeeld patiënten met een hoge verdenking op appendicitis bij presentatie).

Beschouw de patiënt als 'hoog risico' op infectie met SARS-CoV-2 indien 1) de anamnese niet mogelijk is en 2) indien er een indicatie voor een PCR test is, maar het resultaat van de PCR test niet beschikbaar is voor de operatie. Neem voorzorgmaatregelen volgens het lokaal geldende protocol.

Aanbeveling bij positieve PCR test

Overweeg de operatie 14 dagen uit te stellen na een positieve PCR test. Overweeg en bespreek alternatieven voor chirurgie (voor zover deze aanwezig zijn) met de patiënt.

Indien de patiënt asymptomatisch blijft gedurende deze 14 dagen, dan is een preoperatieve PCR test niet opnieuw geïndiceerd.

Indien de patiënt klachten ontwikkelt gedurende deze 14 dagen, overweeg vervolgstappen te bespreken in een multidisciplinair team met de behandelend chirurg, internist-infectioloog, longarts, anesthesioloog zo nodig de intensivist voordat de patiënt opnieuw ingepland wordt voor chirurgie.

Aanbeveling bij herhaalde chirurgie in een beperkte tijdsperiode

Overweeg de patiënt slechts éénmalig te testen door middel van PCR indien de patiënt tijdens opname in korte tijd meerdere operaties ondergaat.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De huidige literatuurzoekactie leverde één relevant artikel op (Doglietto, 2020). Uit het artikel van Doglietto (2020) komt naar voren dat bij een bewezen SARS-CoV-2 infectie er meer kans op complicaties lijkt te zijn. Voor de andere uitkomsten, mortaliteit en ziekenhuisopname, is de bewijskracht zeer laag waardoor er geen conclusies aan te verbinden zijn. De studie includeerde oude patiënten (gemiddelde leeftijd 76 jaar) waarvan de overgrote meerderheid een operatie-indicatie had die geen uitstel toe liet. Het wordt uit het artikel niet duidelijk hoeveel SARS-CoV-2 positieve patiënten voorafgaand aan de operatie klachten hadden. SARS-CoV-2 positieve patiënten werden tussen 23 februari en 1 april retrospectief geïnccludeerd. Tot 8 maart werden patiënten 'generally screened' en na die datum werden patiënten systematisch gescreend op COVID-19, wat impliceert dat een deel van de PCR-positieve patiënten geen klachten wijzend op COVID-19 voorafgaand aan de operatie ervaarde. Er zijn geen artikelen geïdentificeerd die wel of niet pre-operatief screenen met elkaar vergeleken (PICO-1).

In een Nederlandse studie (Jonker, 2020) werden 123 SARS-CoV-2 positieve patiënten die een operatie voor uiteenlopende indicaties ondergingen na propensity matching vergeleken met 196 SARS-CoV-2 negatieve patiënten. De cohorten werden gematched aan de hand van o.a. geslacht, leeftijd, preoperatieve comorbiditeit, ECOG performance status, ASA classificatie, type anesthesie en chirurgisch risico. De mediane leeftijd van de SARS-CoV-2 positieve patiënten bedroeg 72 jaar en de meerderheid van de SARS-CoV-2 positieve patiënten ervaarden COVID-19 symptomen zoals koorts, hoesten, vermoeidheid, dyspneu en buikpijn (respectievelijk 58%, 52%, 46%, 41% en 23%; percentages gebaseerd op ongematched SARS-CoV-2 positieve cohort). Ook rapporteerde de studie dat een deel van de patiënten als behandeling voor SARS-CoV-2 besmetting beademd werd middels een endotracheale tube. Net zoals de studie van Doglietto (2020) rapporteerde deze studie dat de SARS-CoV-2 positieve patiënten een hogere Comprehensive Complication Index hadden vergeleken met gematchede negatieve controles (21 [IQR 0 – 40]) vs 0 [IQR 0 – 12], $p < 0,001$). Echter, de studie includeerde in de SARS-CoV-2 positieve groep patiënten met een positieve PCR van 30 dagen voor de ingreep tot 30 dagen na de operatie. Dit valt buiten de gehanteerde inclusiecriteria waardoor

deze studie niet is opgenomen in de literatuursamenvatting. De onderzoekers voerden een subgroepanalyse uit met patiënten waarbij SARS-CoV-2 binnen zeven dagen vóór of na de operatie was vastgesteld werden vergeleken met *ongematchede* SARS-CoV-2 negatieve patiënten. Er zijn geen baselinekarakteristieken voor deze subgroep beschreven. De 30-daagse postoperatieve mortaliteitsrisico bedroeg 12% (n=8) in de SARS-CoV-2 positieve groep en 4% (n=14) in de SARS-CoV-2 negatieve groep ($p=0,009$).

Een internationaal, multicenter, prospectief cohort studie onderzocht de timing van de operatie na SARS-CoV-2 infectie en 30-dagen mortaliteit en 30-dagen pulmonaire postoperatieve complicaties (COVIDSurg Collaborative and GlobalSurg Collaborative, 2021). Ziekenhuizen leverden achtereenvolgende, geanonimiseerde gegevens aan van patiënten die electieve of spoedoperaties ondergingen. De studie definieerde SARS-CoV-2 infectie vermoedelijk op basis van infectiestatus bepaald in de weken voorafgaand aan de operatie en niet naar aanleiding van een screeningsprocedure naar SARS-CoV-2 in het ziekenhuis. Daarmee voldoet de studie niet aan de inclusiecriteria waardoor deze niet is opgenomen in de literatuursamenvatting. De tijd van diagnose tot de dag van de operatie werd gecategoriseerd in 0-2 weken, 3-4 weken, 5-6 weken en ≥ 7 weken. Pulmonaire postoperatieve complicaties was een samengestelde uitkomst op basis van pneumonie, acute respiratory distress syndrome (ARDS) en/of onverwachte postoperatieve beademing.

In totaal werden 1.384 asymptomatische patiënten vergeleken met 137.104 patiënten die geen SARS-CoV-2 infectie hadden gehad. Patiënten die 0-2 weken, 3-4 weken of 5-6 weken voorafgaand aan de operatie SARS-CoV-2 positief waren getest maar asymptomatisch bleven, hadden in een gecorrigeerd model een groter risico op postoperatieve pulmonaire complicaties vergeleken met patiënten die meer dan 7 weken voor de operatie SARS-CoV-2 positief bleken (respectievelijk 5,2% [3,8-6,6%], 6.1% [4,0-8,3%], 5.4% [3,1-7,7%]; geen SARS-CoV-2 infectie: 2.0% [1,2-2,9%]). Statistisch gezien bevat dit model echter te veel confounders voor het zeer geringe aantal cases om deze conclusie te trekken. Het aantal patiënten die in deze studie asymptomatisch SARS-CoV-2 hadden, is bijzonder hoog ten opzichte van patiënten die wél klachten hadden ervaren (1.384 t.o.v. 1.726), waardoor men zich af kan vragen hoe goed de klachten uitgevraagd en gedocumenteerd zijn en of er mogelijk sprake is van recall bias.

In het onderzoek van Doglietto (2020) was de gemiddelde leeftijd van patiënten met een SARS-CoV-2 infectie 76 jaar en in het onderzoek van Jonker werd gezien dat $>90\%$ van de mortaliteit bij patiënten >70 jaar plaatsvond. Ook de gegevens van de CDC laten zien dat naar mate de leeftijd stijgt, de kans op hospitalisatie en overlijden ook toeneemt: de kans op overlijden t.g.v. COVID-19 neemt enorm toe met het stijgen van de leeftijd; 65 – 74 jaar: 90 keer, 75 – 84 jaar: 220 keer, 85 + jaar: 630 keer) (Center for Disease Control and Prevention).

Knisely (2020) was een retrospectieve studie uitgevoerd onder patiënten die een spoed of semi-spoed operatie voor uiteenlopende indicaties ondergingen in twee ziekenhuizen in New York in de periode medio maart 2020 tot medio april 2020. Per 1 april werden patiënten gescreend op SARS-CoV-2 middels PCR, tenzij de chirurg anders besloot. De studie rapporteerde geen verdere informatie over welke redenen patiënten wel of niet werden gescreend. 36 positieve SARS-CoV-2 patiënten en 432 negatieve patiënten werden geïncludeerd in de studie. De studie onderzocht de associatie tussen SARS-CoV-2 positieve status en IC opname, ernstige complicaties en mortaliteit in het ziekenhuis. Ernstige complicaties werden gedefinieerd als myocard infarct, hartstilstand, shock, respiratoir falen, beroerte, veneuze trombo-embolie maar ook

pneumonie. In een multivariabel model, gecorrigeerd voor leeftijd, geslacht, comorbiditeit, functionele status (onafhankelijk/[deels] afhankelijk), ASA klasse, urgentie van de operatie (spoed/semi-spoed), was SARS-CoV-2 geassocieerd met een verhoogd risico op ernstige complicaties (RR: 7,02; 95% BI: 4,96–9,92). Vijftig procent van de SARS-CoV-2 positieve patiënten ontwikkelden een pneumonie, vergeleken met 3% van de negatieve patiënten. SARS-CoV-2 positieve status was tevens geassocieerd met mortaliteit (RR: 9,29; 95% BI 5,68–15,21). Echter, dit model kon enkel gecorrigeerd worden met één variabele (confounder) gezien het lage aantal gevallen. SARS-CoV-2 positieve status was niet geassocieerd met IC opname in een multivariabel model. 47% van de SARS-CoV-2 positieve patiënten ervaarden klachten zoals koorts, spierpijn, vermoeidheid, hoesten, dyspneu, zere keel, diarree, pijn op de borst, anosmie en/of smaakverlies. Daarnaast includeerde de studie in de SARS-CoV-2 positieve groep patiënten die 21 dagen vóór als 21 dagen ná de operatie positief bleken te zijn, hetgeen buiten de inclusiecriteria valt waardoor deze studie niet is opgenomen in de literatuursamenvatting. De onderzoekers voerden een subgroepanalyse uit met patiënten waarbij SARS-CoV-2 binnen 14 dagen vóór of na de operatie was vastgesteld werden vergeleken met SARS-CoV-2 negatieve patiënten. Dit werd echter niet onderzocht in een multivariabel model. SARS-CoV-2 patiënten mét klachten hadden meer risico op ernstige complicaties vergeleken SARS-CoV-2 patiënten zonder klachten (94,1% t.o.v. 26,3%; *p-waarde* < 0,0001). De studie rapporteerde niet over de associatie tussen SARS-CoV-2 patiënten zonder klachten en ernstige complicaties vergeleken met SARS-CoV-2 negatieve patiënten. Uit de systematische literatuurzoekactie kwam één artikel naar voren die asymptomatische patiënten met een positieve PCR-test includeerde en vergeleek met patiënten die geen SARS-CoV-2 besmetting hadden (Barkordari, 2020). De onderzoekers rapporteerden een hogere mortaliteit en langere opnameduur op de intensive care voor de PCR positieve groep. De studie zou PCR positieve patiënten hebben gematched met de controlepatiënten, maar verdere beschrijving van deze procedure ontbreekt. De summiere baselinekarakteristieken die worden vermeld suggereren dat er niet is gematched op relevante prognostische factoren, waardoor het artikel is geëxcludeerd voor de literatuursamenvatting.

Uit de andere studies die zijn beoordeeld voor deze module komt eveneens naar voren dat symptomatische COVID-19 in de perioperatieve fase mogelijk bijdraagt aan een slechtere uitkomst. Helaas wordt in geen van deze artikelen rekening gehouden met confounding (Ayhan, 2020; Dowlati, 2020; Ego, 2020; Kayani, 2020; LeBrun, 2020 zie exclusietabel) waardoor deze studies een vertekend resultaat kunnen geven. Een andere studie werd geëxcludeerd vanwege het ontbreken van een controlegroep (CovidSurg, zie exclusietabel).

Samenvattend, patiënten met SARS-CoV-2 die een operatie ondergaan lijken een verhoogd risico te hebben op postoperatieve complicaties. De bestaande literatuur differentieert echter niet voldoende de uitkomsten naar patiënten die geen klachten hadden voorafgaand aan de operatie, waardoor het lastig is een conclusie te geven over het exacte risico van een pre-/asymptomatische infectie met SARS-CoV-2 op postoperatieve complicaties. Wel zijn er aanwijzingen in algemene zin dat naar mate patiënten ouder zijn, de kans op hospitalisatie en mortaliteit ten gevolge van COVID-19 enorm toeneemt.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Screenen op SARS-CoV-2 infectie middels anamnese is niet belastend voor de patiënt in tegenstelling tot het afnemen van een nasofaryngeale PCR-test. Potentiële nadelen van screenen middels anamnese zijn dat het voor sommige patiënten mogelijk lastig in te schatten zal zijn in hoeverre zij COVID-19 symptomen ervaren en er een mogelijkheid bestaat dat enkele patiënten symptomen verzwijgen zodat de operatie waar ze zich op in

hebben gesteld doorgang kan vinden. Potentiële nadelen van screening middels nasofaryngeale PCR voor de patiënt zijn 1) onplezierige afname van testmateriaal, 2) dat de patiënt een extra keer naar de locatie dient te komen en 3) onnodige uitstel van operatie bij vals-positieve test (indien rest RNA wordt aangetoond [post-COVID blip]). De systematische literatuursamenvatting laat echter zien dat er voor oudere patiënten met COVID-19 er een reëel risico lijkt te bestaan op ernstige postoperatieve complicaties waardoor de werkgroep van mening is dat de patiënt daarvoor behoed dient te worden.

Kosten (middelenbeslag)

Pre-operatief screenen middels PCR brengt meer kosten met zich mee (testmateriaal, personeel) dan enkel screenen middels anamnese. Echter, niet screenen middels PCR zal kunnen leiden tot meer postoperatieve complicaties hetgeen ook hoge kosten met zich meebrengt.

Aanvaardbaarheid, haalbaarheid en implementatie

Uit de SCOUT-studie is naar voren gekomen dat tijdens de vorige periode waarin veel patiënten zijn opgenomen, het percentage patiënten die SARS-CoV-2 positief waren zonder klachten rond de 1,5% lag. Het is aannemelijk dat bij nieuwe periodes met een hoge prevalentie van SARS-CoV-2 infecties een deel van de patiënten die geopereerd wordt zonder klachten bij anamnese toch SARS-CoV-2 positief is.

Het implementeren van screening van preoperatieve patiënten middels PCR brengt meer obstakels met zich mee dan screenen middels anamnese. Anamnese afnemen kan telefonisch, terwijl het afnemen van een nasofaryngeale PCR-test op locatie dient te gebeuren. Dit vraagt om ingrijpende logistieke aanpassingen en inzet van personeel. Daarnaast kampen sommige ziekenhuizen met beperkte testcapaciteit. Screening van chirurgische patiënten middels PCR zou er dan toe kunnen leiden dat andere patiëntengroepen niet of later getest kunnen worden.

De werkgroep is van mening dat indien ≥ 2 weken na de eerste positieve PCR-test er wederom een positieve testuitslag is, de Ct waarde mogelijk richting kan bieden in het verdere beleid. Een mogelijke strategie zou zijn om bij een waarde boven het 90^e percentiel, de operatie doorgang te laten vinden. Bij een Ct waarde lager dan het 90^e percentiel, kan serologie mogelijk handvatten geven evenals overleg in een MDO.

De werkgroep is van mening dat bij personen die volledig zijn ingeënt, er geen pre-operatieve screening middels PCR-test uitgevoerd hoeft te worden. Een vaccinatie biedt weliswaar geen 100% bescherming tegen SARS-CoV-2 gerelateerde klachten, echter het aantal gevaccineerde personen die pre-operatief gescreend zouden moeten worden om bij één patiënt een SARS-CoV-2 gerelateerde post-operatieve complicatie te voorkomen, ligt dermate hoog dat de werkgroep pre-operatieve screening niet doelmatig acht en dus niet gerechtvaardigd vindt. Voor criteria omtrent volledige vaccinatie verwijst de werkgroep naar de website van het [RIVM](#). Eventueel kan men vragen om een vaccinatiebewijs. Men kan hierbij benadrukken dat dit wordt gevraagd in belang van de patiënt.

Tijdens de eerste periode van hoge prevalentie COVID-19 en belasting van het zorgsysteem, bleek de prevalentie niet gelijk verdeeld over het land, waardoor regio's met weinig ziektegevallen zich niet genoodzaakt voelden om het advies tot screening te volgen. De werkgroep heeft hier notie van genomen en heeft getracht om hier een adequate maat voor te gebruiken. De werkgroep heeft gekozen om de

aanbeveling te linken aan de risiconiveaus per veiligheidsregio conform het dashboard coronavirus van de rijksoverheid (waakzaam, zorgelijk, ernstig, zeer ernstig, lockdown). Regio's die een lagere prevalentie COVID-19 hebben hoeven dan minder stringente maatregelen te implementeren.

Voor pijler 2 (risico zorgmedewerkers) en 3 (risico medewerkers) wordt verwezen naar de leidraad 'Persoonlijke bescherming in de (poli)klinische setting vanwege SARS-CoV-2' en de leidraad 'Perioperatieve zorg infectiepreventie ten tijde van COVID-19 pandemie'.

Het is van groot belang dat de maatregelen zoals in de leidraad PBM worden geadviseerd ook daadwerkelijk worden nageleefd. Op deze manier wordt de kans op ongewenste transmissie van SARS-CoV-2 aanzienlijk teruggebracht in het perioperatieve traject.

Dit alles laat onverlet dat wanneer het niet mogelijk is om aan de voorwaarden zoals gesteld in de leidraad PBM te voldoen, preoperatieve screening middels PCR op SARS-CoV-2 op lokaal niveau een alternatief is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Uit de literatuur komt naar voren dat patiënten met SARS-CoV-2 die een operatie ondergaan een verhoogd risico lijken te hebben op postoperatieve complicaties. De bestaande literatuur differentieert echter niet de uitkomsten naar patiënten die geen klachten hadden voorafgaand aan de operatie waardoor het lastig is een conclusie te geven over het exacte risico van een pre-/asymptomatische infectie met SARS-CoV-2 op postoperatieve complicaties. Wel zijn er aanwijzingen in algemene zin dat naar mate patiënten ouder zijn, de kans op hospitalisatie en mortaliteit ten gevolge van COVID-19 enorm toeneemt.

Screenen middels een nasofaryngeale PCR-test geeft een hogere belasting voor de patiënt ten opzichte van anamnese. De werkgroep is van mening dat met name voor oudere patiënten het reële risico op ernstige postoperatieve complicaties deze extra belasting rechtvaardigt. Daarnaast is er een mogelijkheid dat enkele patiënten symptomen verzwijgen zodat de operatie waar ze zich op in hebben gesteld doorgang kan vinden, waardoor screenen middels louter anamnese risico's met zich meebrengt.

Gezien de hogere opbrengst van screening bij een hogere incidentie van ziektegevallen, heeft de werkgroep ervoor gekozen om de aanbeveling te linken aan de risiconiveaus per veiligheidsregio conform het dashboard coronavirus van de rijksoverheid (waakzaam, zorgelijk, ernstig, zeer ernstig, lockdown) en aan te passen naar de leeftijd van de te opereren patiënt. Pre-operatieve screening middels PCR-test bij volledig gevaccineerden acht de werkgroep niet doelmatig en gerechtvaardigd.

Het is van groot belang dat de maatregelen zoals gesteld in leidraad PBM worden nageleefd. Indien dit niet of onvoldoende mogelijk is, kan het uitbreiden van de indicatie preoperatieve screening middels PCR op SARS-CoV-2 op lokaal niveau een alternatief zijn.

De werkgroep is van mening dat bij personen die volledig zijn ingeënt, er geen pre-operatieve screening middels PCR-test uitgevoerd hoeft te worden. Een vaccinatie biedt weliswaar geen 100% bescherming tegen SARS-CoV-2 gerelateerde klachten, echter het aantal gevaccineerde personen die pre-operatief gescreend zouden moeten worden om bij één patiënt een SARS-CoV-2 gerelateerde post-operatieve complicatie te voorkomen, ligt dermate hoog dat de werkgroep pre-operatieve screening niet doelmatig acht en dus niet

gerechtvaardigd vindt. Voor criteria omtrent volledige vaccinatie verwijst de werkgroep naar de website van het RIVM. Eventueel kan men vragen om een vaccinatiebewijs. Men kan hierbij benadrukken dat dit wordt gevraagd in belang van de patiënt.

Het beschermende effect van vaccins tegen een ernstig ziekte beloop na een operatie is onduidelijk. In November 2021 heeft de Gezondheidsraad geadviseerd om een booster prik toe te voegen aan het huidige vaccinatie schema, gezien de afname van vaccin effectiviteit bij oudere leeftijdsgroepen over de tijd. Hiernaast is vaccin effectiviteit tegen ernstige ziekte onbekend in het licht van de opkomst van nieuwe SARS-CoV-2 varianten (omikron). In vitro onderzoek (ongepubliceerde data) suggereert dat sera van gevaccineerde patiënten verminderd neutraliserend vermogen hebben tegen omikron in vergelijking met andere SARS-CoV-2 varianten (Cele, 2021; Wilhelm, 2021; Pfizer and Biontech update on omicron variant, 8-12-2021). Het neutraliserende effect tegen omikron van sera van geboosterde patiënten was significant hoger dan van ongeboosterde patiënten.

Gezien de afname van vaccineffectiviteit over de tijd, en de opkomst van nieuwe virusvarianten, is de werkgroep van mening dat pre-operatieve screening wel nodig is bij patiënten van 65 jaar en ouder die niet volledig gevaccineerd zijn, en dat volledig vaccinatie inhoudt: inclusief een booster.

Onderbouwing

Achtergrond

Tijdens de initiële uitbraak van COVID-19 heeft deze commissie de leidraad 'pre-operatieve diagnostiek naar SARS-CoV-2 infectie bij asymptomatische patiënten ingepland voor chirurgie onder algehele anesthesie' gepubliceerd. In deze leidraad werd geadviseerd om patiënten preoperatief te testen op de aanwezigheid van SARS-CoV-2 indien het aantal opnames van COVID-patiënten in een Nederlands ziekenhuis hoger is dan 40 nieuwe per dag gemiddeld over drie dagen (gebaseerd op het dashboard coronavirus van de Rijksoverheid). Ten tijde van het schrijven van de leidraad was er vrijwel geen literatuur beschikbaar die gebruikt kon worden om tot een goed gefundeerd advies te komen. In de afgelopen maanden is meer duidelijk geworden over het gedrag van het virus, de manier van behandelen van patiënten met COVID-19, maar ook is er enig zicht op de effecten van COVID-19 op operatieve uitkomsten.

De leidraad was gestoeld op de volgende drie pijlers:

- *Pijler 1:* Patiënten kunnen ten tijde van de operatie asymptomatisch zijn of zich in de incubatieperiode bevinden en vervolgens postoperatief COVID-19 klachten ontwikkelen waardoor er een verhoogd risico op post-operatieve complicaties bestaat (Arminian, 2020; Lei, 2020; Li Y, 2020; COVIDSurg Collaborative).
- *Pijler 2:* Asymptomatische/mild symptomatische patiënten kunnen besmettelijk zijn, waardoor zorgverleners risico lopen op besmetting met SARS-CoV-2, met name gedurende aerosolgenererende handelingen (Heinzerling, 2020; Heneghan, 2020; Li, 2020).
- *Pijler 3:* Asymptomatische/mild symptomatische patiënten kunnen besmettelijk zijn, waardoor medepatiënten risico lopen op besmetting met SARS-CoV-2. Deze medepatiënten hebben relatief vaak een hogere leeftijd en multimorbiditeit hetgeen risicofactoren zijn voor een ongunstig beloop van COVID-19 (Li Y, 2020; Yang, 2020; Zou, 2020).

Voor adviezen aangaande de bescherming van zowel patiënten als zorgmedewerkers tegen accidentele besmetting met SARS-CoV-2 (pijler 2 en 3) verwijst de commissie naar de onderbouwing en adviezen in de leidraad 'Persoonlijke bescherming in de (poli)klinische setting' en de leidraad 'Perioperatieve zorg infectiepreventie ten tijde van COVID-19 pandemie'.

Om te onderzoeken wat de effecten zijn van een asymptomatische of presymptomatische infectie met SARS-CoV-2 op postoperatieve uitkomsten (pijler 1) is er opnieuw systematische literatuurzoekactie uitgevoerd en een literatuursamenvatting geschreven.

Afbakening van de richtlijnmodule

Deze richtlijnmodule is gericht op patiënten die anamnestiche geen klachten hebben die wijzen op een SARS-CoV-2 infectie. Indien de patiënt wel klachten heeft dient een patiënt getest te worden op de aanwezigheid van SARS-CoV-2. Indien er sprake is van een positieve PCR op SARS-CoV-2 adviseert de commissie electieve operaties zes weken en semi-electieve twee weken (gerekend vanaf het moment dat patiënten klachtenvrij zijn) uit te stellen (Taylor, 2015; Long, 2019).

Deze richtlijnmodule is niet van toepassing op zwangere vrouwen en kinderen. Voor adviezen rondom screening van kinderen verwijst de werkgroep naar de leidraad 'Pre-operatieve diagnostiek naar COVID-19 bij asymptomatische kinderen ingepland voor chirurgie onder algehele anesthesie'.

De richtlijnmodule is gericht op operaties onder algehele anesthesie. Indien er een reële kans bestaat dat conversie nodig is van regionale anesthesie naar algehele anesthesie kan besloten worden onderstaande adviezen rondom pre-operatieve screening te volgen. Deze risico-inschatting kan gemaakt te worden door het opererend team en wordt besproken met de patiënt.

Conclusies / Summary of Findings

Low GRADE	<u>Comprehensive Complication Index (continuous version of Clavien-Dindo classification)</u> Patients with preoperative SARS-CoV-2 infection who undergo surgery may have more postoperative complications than patients who do not have a preoperative SARS-CoV-2 infection. <i>Source: Doglietto (2020)</i>
Very low GRADE	<u>Mortality, hospital admission duration</u> It is uncertain whether SARS-CoV-2 infection during surgery is associated with increased mortality and hospital admission duration. <i>Source: Doglietto (2020)</i>

Samenvatting literatuur

Doglietto (2020) was a retrospective cohort study from Brescia, Italy that evaluated early surgical mortality and complication rates in SARS-CoV-2 positive patients as compared to matched surgical patients without SARS-CoV-2. Patients who underwent general, vascular, thoracic, orthopedic and neuro-surgical treatment

from February 23 to April 1, 2020, and who had either a positive result for SARS-CoV-2 preoperatively or developed a positive result within 1 week after surgery were included in the study. Patients were systematically screened for SARS-CoV-2 before surgery after March 8, 2020. Screening for SARS-CoV-2 was performed with RT-PCR on nasopharyngeal swabs; chest radiography and/or computed tomography (CT) were performed to investigate lung abnormalities. Diagnosis of infection with SARS-CoV-2 was based on positivity of at least one of these investigations. Patients with SARS-CoV-2 infection were matched with patients without infection with a 1:2 ratio for surgical pathology with identical treatment by the same team, sex, age group, American Society of Anesthesiologists (ASA) score, and comorbidities, as recorded in the surgical risk calculator of the American College of Surgeons National Surgical Quality Improvement Program. Patients older than 65 years were also matched for Clinical Frailty Scale score. Gynecologic and minor surgical procedures were excluded.

Of the 41 patients COVID-19 patients, 33 were positive for SARS CoV-2 preoperatively (80.5%) and 8 (19.5%) had positive results for infection within 5 days after surgery. The study did not report how many patients experienced COVID-19 symptoms preoperatively. Most patients with COVID-19 were matched with historical controls, as only 11 controls were identified during the same study period. Most baseline features were similar between COVID-19 positive and negative patients. However, systemic sepsis, ventilator dependency and, to a lesser extent, dyspnea at baseline were different between the groups. The mean age was relatively high - 76 and 77 years for COVID-positive and negative patients, respectively.

The study results are depicted in *Table 1*. Mortality, Comprehensive Complication Index (CCI, continuous version of Clavien-Dindo classification; grades all complications, not only the most severe one) and thrombotic and pulmonary complications were significantly higher in the COVID-19 groups as compared to controls (*mortality*: OR, 9.5 [95% CI, 1.77-96.53]; *CCI*: OR, 4.98 [95% CI, 1.81-16.07]; *thrombotic complications*: OR, 13.2 [95% CI, 1.48-∞]; *pulmonary complications*: OR, 35.6 [95% CI, 9.34-205.55]).

However, it is important to note that these comparisons were not adjusted for baseline characteristics. Only CCI was studied in a multivariable ordinal model. After adjusting for age and respiratory function at baseline, patients with COVID-19 were 13,3 times more likely to have post-operative complications than patients without COVID-19. Because death was an extremely unbalanced variable (death, 8.1%, vs discharged, 91.9%), the authors did not model this outcome. Half of the procedures were performed under general anesthesia. Outcomes were not stratified for patients who received general anesthesia versus local anesthesia.

Table 1. Baseline characteristics and outcomes of Doglietto (2020)

Baseline characteristics			Outcomes			
	COVID-19 positive	COVID-19 negative	<u>Cumulative Link Model for outcome</u> <u>Comprehensive Complication Index (CCI), OR (95% CI)</u> COVID-19: 13.29 (5.09-34.68) Age: 1.04 (1.01-1.07) Respiratory function at admission: Poor: 3.35 (0.36-31.62) Good: 0.38 (0.16-0.94) –			
n=	41	82	<u>Bivariate analysis</u>			
Age, mean (SD):	75.95 (15.17)	76.93 (14.08)		COVID-19 positive	COVID-19 negative	
Sex, women	56%	67%	Complication, n (%)			
Emergency	83%	77%	Trombotic	4 (9.8) ¹	0	0.004
ASA			Hemorrhagic	15 (36.6)	32 (39.0)	0.79
I	1 (2.44)	2 (2.44)	Pulmonary			<0.001
II	3 (7.32)	7 (8.54)	Pneumonia	18 (44)	2 (2.4)	
III	19 (46.34)	48 (58.54)	ARF	6 (14.6)	1 (1.20)	
IV-V	18 (43.90)	25 (30.49)	Cardiac			0.10
Systemic sepsis <48 h before surgery			Atrial fibrillation	0	1	
Sepsis	4 (9.76)	6 (7.32)	Shock	2 (4.9)	0	
Septic shock	3 (7.32)	0	CCI, median (IQR)	29.6 (20.9-53.2)	14.8 (0.0-20.9)	<0.001
SIRS	1 (2.44)	0	Days in hospital, mean (SD)	0.9 (2.9)	0.4 (1.6)	0.52
Frailty Score, mean (SD)	4.10 (1.87)	4.23 (1.78)	Death, n (%)	8 (19.5)	2 (2.4)	0.001
Anesthesia			¹ peripheral thrombosis on postoperative day (POD)			
General	20 (48.78)	43 (52.44)	4 and 3 arterial thromboses on POD 1 after			
Local	21 (51.22)	39 (47.56)	thromboembolectomy for acute lower limb ischemia			
Ventilator dependency	3 (7)	0				
Dyspnea						
No	25 (85)	73 (89)				
Moderate	3 (7)	8 (10)				
At rest	3 (7)	1 (1)				

Abbreviations: ASA: American Society of Anesthesiologists (ASA) class; CI confidence interval; IQR, interquartile range; SD standard deviation; SIRS systemic inflammatory response syndrome

Level of evidence of the literature

The level of evidence regarding the outcome measure Comprehensive Complication Index were downgraded by two levels because of study limitations (risk of bias, see risk of bias assessment) and number of included patients (imprecision).

The level of evidence regarding the outcomes mortality and hospital admission duration were downgraded by three levels because of study limitations (risk of bias by two levels, see risk of bias assessment) and number of included patients (imprecision).

Zoeken en selecteren

The guideline development group performed a systematic review of the literature in order to answer the following questions:

1. Does diagnostic screening for SARS-CoV-2 of patients who undergo surgery result in less negative postoperative outcomes?

PICO 1:

P: patients who undergo surgery

I: screening with a COVID-19 diagnostic test (PCR)

C: no screening/history taking

O: postoperative outcomes

2. Is a pre-symptomatic/asymptomatic SARS-CoV-2 infection associated with negative outcomes in patients who undergo surgery?

PICO 2:

P: patients who undergo surgery

I: (presymptomatic/asymptomatic) infection with SARS-CoV-2

C: no infection with SARS-CoV-2

O: postoperative outcomes

To be included in the literature summary for PICO 2, articles had to include a multivariable model or had to adjust for confounding by (propensity) matching. The guideline development group also decided to include studies that investigated postoperative outcomes in patients with SARS-CoV-2 infection who had symptoms and studies that included patients that received local anesthesia. Because patients without symptoms may become RT-PCR/chest CT positive a few days after infection, the guideline development group also decided to include studies with patients that received a positive test results within a 7-day post-operative period. The working group defined SARS-CoV-2 infection as having a positive SARS-CoV-2 RT-PCR and/or suspicious chest CT (as defined in the studies).

Relevant outcome measures

The guideline development group considered mortality and post-operative complications to be critical outcome measures for decision making; hospital admission duration was considered an important outcome measure for decision making.

A priori, the working group did not define the outcome complications but used the definitions employed in the studies.

The guideline development groups defined clinically relevant differences as follows:

Mortality: default boundaries for clinically relevant differences, i.e. RR/OR > 1.25 or <0.80 (GRADE working group)

Complications: lethal <5%, acute or severe <25% (absolute difference)

Hospital admission duration: ≥1 day

Search and select (Methods)

We searched the databases PubMed (includes preprint from Medrxiv) and Embase with relevant search terms up to November 25 2020. Until June 9 2020, the databases Google Scholar, Medrxiv and WHO database were also searched. The detailed search strategy is described in the Appendix. After reading the full text articles, 23 studies were excluded from the literature summary (see the table with reasons for exclusion under the tab Methods), and one study (PICO 2) was identified and included in the summary of the literature.

Verantwoording

Laatst beoordeeld : 01-02-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Behandeling bij COVID-19

Waar gaan de modules binnen deze richtlijn over?

De modules Behandeling binnen de richtlijn COVID-19 richten zich op wat volgens de huidige maatstaven de beste behandeling is voor patiënten met COVID-19. De volgende onderwerpen komen aan de orde:

- Medicamenteuze behandeling
- Tromboseprofylaxe
- Niet-invasieve ademhalingsondersteuning
- Cardiovasculaire complicaties en cardiovasculaire ziekten covid-19
- Invasieve beademing (volgt binnenkort)

Voor wie zijn deze richtlijnmodules bedoeld?

Deze modules zijn ontwikkeld voor alle leden van de beroepsgroepen die betrokken zijn bij de behandeling van COVID-19.

Voor patiënten

Deze modules helpen artsen bij het behandelen van patiënten met COVID-19 binnen het ziekenhuis. Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over COVID-19.

Hoe zijn de richtlijnmodules tot stand gekomen?

Na de uitbraak van SARS-COV-2 zijn er binnen het programma COVID-19 een groot aantal leidraden en handreikingen ontwikkeld en gepubliceerd op de website van de Federatie Medisch Specialisten. Deze leidraden en handreikingen zijn doorontwikkeld tot richtlijnmodules. Voor de totstandkoming per onderwerp verwijzen we naar de startpagina van de verschillende modules.

Status van de richtlijn

Gedurende de pandemie zijn diverse leidraden gepubliceerd. Voor onderwerpen die momenteel (nog) niet als modules zijn gepubliceerd, verwijzen we u naar de website:

<https://www.demedischspecialist.nl/onderwerp/details/richtlijnen-handreikingen-leidraden>.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Medicamenteuze behandeling voor patiënten met COVID-19

Waar gaat deze richtlijn over?

Deze richtlijnmodules geven aanbeveling over de beste medicamenteuze behandeling voor patiënten met COVID-19 patiënten. Voor de samenvatting van de richtlijn, [klik hier](#).

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bedoeld voor zorgverleners in de tweede (of derde) lijn betrokken bij de behandeling van patiënten met COVID-19. Daarnaast is de richtlijn ook informatief voor andere zorgverleners.

Voor patiënten

Patiënten kunnen in het ziekenhuis medicijnen krijgen direct gericht tegen het virus, tegen de door het virus veroorzaakte ontstekingen en gericht op het voorkomen van het ontstaan van bloedklonten (trombose of longembolie). Er bestaan nog geen medicijnen die iemand zeer snel kunnen genezen van corona. Het lichaam moet dit vooral zelf doen. Medicijnen kunnen het lichaam hierbij helpen. In deze modules worden adviezen gegeven over welke medicijnen wel en niet gebruikt kunnen worden.

Zie ook de informatie op [Thuisarts.nl](https://thuisarts.nl).

Hoe is de richtlijn tot stand gekomen?

Bij aanvang van de pandemie in 2020 was het onduidelijk en/of bestaande of nieuwe medicijnen een relevante bijdrage konden leveren aan het herstel van patiënten geïnfecteerd met het SARS-CoV-2. Vandaar dat eind februari 2020 werd aangevangen met de eerste versie van de leidraad 'Medicamenteuze behandeling voor patiënten met COVID-19 (infectie met SARS-CoV-2)', welke begin maart 2020 online beschikbaar werd gesteld op de website van de SWAB (<https://swab.nl/nl/covid-19>). Sindsdien werd het adviesdocument op wekelijkse basis gereviseerd en indien nodig op basis van nieuwe publicaties van onderzoek aangepast. Het initiatief en de coördinatie hiertoe werden genomen door de SWAB Leidraadcommissie, ondersteund door het kennisinstituut van de Federatie Medisch Specialisten en een brede klankbordgroep waarbinnen de betrokken specialisten(verenigingen) zijn vertegenwoordigd. In september 2021 is gestart met het doorontwikkelen van de leidraad naar richtlijnmodules. Daarnaast zijn de modules ook tegengelezen door het 'Expertiseteam Behandeling COVID-19'. Voor de volledige lijst van participerende organisaties verwijzen wij u graag naar de modules.

Samenvatting Medicamenteuze behandeling COVID-19

Voor de samenvatting van de medicamenteuze behandeling voor patiënten met COVID-19 [klik hier](#).

Addendum medicamenteuze behandeling voor patiënten met COVID-19 (flexibel deel - nieuwe orale virusremmers, monoclonale antistoffen, convalescentplasma, e.a.)

Voor de inhoud van het Addendum medicamenteuze behandeling voor patiënten met COVID-19 (flexibel deel) [klik hier](#).

Voor de bijbehorende disclaimer, [klik hier](#).

Hydroxychloroquine

Uitgangsvraag

Wat is de plaats van hydroxychloroquine bij de behandeling van COVID-19 patiënten?

Aanbeveling

Behandel patiënten met COVID-19 niet met hydroxychloroquine.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder hydroxychloroquine bij patiënten met COVID-19. Tot 7 januari 2021 werden er 8 gerandomiseerde gecontroleerde studies (RCT's) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=3037 in de interventiegroep en n=4569 in de controlegroep), waaronder twee grote studies: de RECOVERY trial (Horby, 2020) en de SOLIDARITY trial (Pan, 2020). Drie studies onderzochten hydroxychloroquine in patiënten die niet waren opgenomen in het ziekenhuis (n=500 in de interventiegroep en n=520 in de controlegroep).

Omdat de geïnccludeerde studies verschillende populaties onderzochten, zijn de resultaten opgesplitst in groepen zonder ziekenhuisopname (ambulant) en met ziekenhuisopname. De studies met opgenomen patiënten bevatten daarnaast heterogene patiëntgroepen. Waar mogelijk zijn deze studies opgesplitst voor patiënten met milde, matige en ernstige COVID-19 symptomen op basis van respiratoire ondersteuning bij inclusie. Er werden alleen RCT's geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat er vijf open-label trials waren, met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten, werd de kwaliteit van dit bewijs waar nodig naar beneden bijgesteld. Daarnaast waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. Eventueel werd de kwaliteit van het bewijs naar beneden bijgesteld als er veel heterogeniteit tussen de studies was, bijvoorbeeld in rapportage van de uitkomstmaat. De verschillen in de geïnccludeerde patiënten werden niet meegenomen in de gradering van de studies, maar zullen wel worden meegenomen in de overwegingen.

Studies in patiënten die waren opgenomen in het ziekenhuis

Op basis van de gevonden resultaten wordt er geconcludeerd dat er voor de cruciale uitkomstmaat 'mortaliteit' en 'invasieve respiratoire ondersteuning' geen voordeel is voor behandeling met hydroxychloroquine. De gevonden studies tonen ook geheel consistent géén positief klinisch effect van hydroxychloroquine op duur van ziekenhuisopname of andere uitkomstmaten. Behandeling met hydroxychloroquine resulteert mogelijk zelfs in een hogere mortaliteit (RR 1.09; 95% CI 0.99-1.19) en meer noodzaak voor mechanische ventilatie (RR 1.13; 95% CI 0.95-1.34). De bewijskracht van de cruciale uitkomstmaten binnen patiënten die opgenomen waren in het ziekenhuis komt uit op 'redelijk'.

Studies in patiënten die niet waren opgenomen in het ziekenhuis

Op basis van de gevonden resultaten kan worden geconcludeerd dat er voor de cruciale uitkomstmaat

mortaliteit geen klinisch relevant verschil is gevonden voor behandeling met hydroxychloroquine in vergelijking met behandeling zonder hydroxychloroquine bij patiënten met COVID-19 die niet zijn opgenomen in het ziekenhuis. Ook bij andere relevante uitkomstmaten was er geen overtuigend bewijs in het voordeel van hydroxychloroquine. Echter, de drie studies die hydroxychloroquine onderzochten bij ambulante patiënten waren klein en niet gepowerd om kleine verschillen in bijvoorbeeld mortaliteit vast te stellen. De bewijskracht van de deze uitkomstmaten komt daarom uit op 'laag' of 'zeer laag'.

Aanvulling van literatuur tot 2-9-2021

In aanvulling op bovenstaande literatuur werd er een nieuwe zoekopdracht uitgevoerd op 2 september 2021. Deze zoekopdracht leverde 10 nieuwe RCT's op. Geen van deze studies liet een voordeel van hydroxychloroquine zien ten opzichte van de standaardbehandeling. De grootste RCT bij ambulante (hoog risico) patiënten was de TOGETHER studie, bij opgenomen patiënten was de grootste studie de DisCoVeRy studie, waarin respectievelijk 214 en 145 patiënten werden gerandomiseerd naar hydroxychloroquine. Beide studies werden voortijdig gestaakt. De TOGETHER studie toonde geen voordeel van hydroxychloroquine in tijd totdat patiënten klachten vrij werden, de tijd tot opname in het ziekenhuis of opnameduur. Ook in de DisCoVeRy studie ontbrak een positief effect van hydroxychloroquine op de klinische status na 15 dagen (de primaire uitkomstmaat), gemeten op een 7-puntsschaal, bij een interim analyse (adjusted OR 0.93; 95% CI 0.62-1.41). De mortaliteit na 28 dagen was iets hoger in de hydroxychloroquine-groep: 6.5% versus 5.3%, maar dit was niet statistisch significant. Daarnaast is het artikel van Abd-Elsalam (2020), welke is opgenomen in de literatuuranalyse teruggetrokken door het tijdschrift (Abd-Elsalam: retraction note, 2022). Het weglaten van deze studie uit de gepoolde resultaten, resulteert niet in andere conclusies. Concluderend, de aanbevelingen veranderen niet na een aanvullend literatuuronderzoek.

Overige overwegingen

Bijwerkingen

Ten gevolge van het gebruik van hydroxychloroquine kan cardiotoxiciteit optreden waardoor eerder ECG-monitoring van het QT-interval werd aanbevolen (Nord, 2004; Schrezenmeier, 2020). Er is tevens gepubliceerd dat er een verdubbeling van cardiovasculaire toxiciteit is gezien, wanneer hydroxychloroquine samen gegeven werd met azitromycine (Lane, 2020). In een cohort uit New York werd bij 11% van de patiënten die hydroxychloroquine en azitromycine gelijktijdig toegediend kregen al op dag 3.6 ± 1.6 (SD) na start therapie een QTc > 500 ms geregistreerd (Chorin, 2020). Dat er risico is op QT-tijdverlenging door hydroxychloroquine, waarbij dat risico nog verder toeneemt als er azitromycine aan toe werd gevoegd, bleek ook uit een andere Amerikaanse patiënten serie (Mercuro, 2020). Bij milde tot matig ernstige ziekte was het risico op QTc-tijd verlenging door hydroxychloroquine significant hoger in vergelijking met SOC (14.6 % vs. 1.7%), maar in deze studie verhoogde de combinatie met azitromycine het risico niet verder (14.7%; Cavalcanti, 2020).

Ook meerdere RCT's die geëvalueerd werden in de huidige richtlijn beschrijven cardiale toxiciteit van opgenomen patiënten (Chen, 2020; RECOVERY trial (Horby, 2020); Self, 2020; Ulrich, 2020 (TEACH)). De RECOVERY trial (Horby, 2020) rapporteerde dat ritmestoornissen, onder andere supraventriculaire tachycardie, ventriculaire tachycardie of fibrillatie en atrioventriculaire blokkade die interventie behoefde, optraden in 60 van de 735 (8.2%) patiënten in de interventiegroep en in 90 van de 1420 (6.3%) patiënten in de controlegroep (RR 1.29; 95% CI 0.94 tot 1.76). Self (2020) rapporteerde een incidentie van ventriculaire tachycardie/fibrillatie van 5/242 (2%) in de interventiegroep, vergeleken met 6/237 (2.5%) in de

controlegroep (RR 0.82, 95% CI 0.25 tot 2.64). De incidentie van *cardiac arrest* was in deze studie 10/242 (4.1%) in de interventiegroep en 4/237 (1.7%) in de controlegroep (RR 2.45; 95% CI 0.78 tot 7.70; adjusted OR 2.51; 95% CI 0.78 tot 8.12). In de studie van Chen en Ulrich werden geen ritmestoornissen gezien, maar bij deze laatste studie werd er wel frequenter een verlenging van het QT-interval >500 ms gezien (3/67 (4.5%) in de interventiegroep ten opzichte van 1/61 (1.6%) in de controlegroep (RR 2.73; 95% CI 0.29 tot 25.57)).

Al met al tonen meerdere studies een klinisch relevant percentage ernstige bijwerkingen, met name cardiale geleidingsstoornissen, die eventueel de sterfte kunnen verhogen. Ook Cochrane review toont dat behandeling met hydroxychloroquine negatief kan werken. Zij bekeken studies tot februari 2021 en concludeerden op basis van 6 trials dat er een 3 keer verhoogde kans was op bijwerkingen in de hydroxychloroquine groep (RR 2.90, 95% CI 1.49 tot 5.64), maar geen verschil in de kans op ernstige bijwerkingen.

Dosering

Farmacokinetische simulatiestudies voorspelden een adequate longconcentratie met een dosering van 2 x 400 mg hydroxychloroquine sulfaat op dag 1, gevolgd door 2 x 200 mg hydroxychloroquine sulfaat op dag 2-5. Dit is dezelfde dosering die in een van de eerste versies van de SWAB-leidraad medicamenteuze behandelopties van COVID-19 stond. Er werd gecalculeerd dat een oplaaddosis nodig is om in korte tijd een effectieve dosering te kunnen bereiken (Perinal, 2020). Het Engelse gerandomiseerde RECOVERY onderzoek gebruikte een veel hogere dosering gedurende 10 dagen: 2400 mg in de eerste 24 uur verdeeld over 4 giften en nog 9 dagen 2 dd 400 mg. Omdat er bij deze hogere dosering nog altijd geen effect werd gezien op klinische eindpunten als overlijden op dag 28, zijn er geen aanvullende positieve effecten van een andere dosering te verwachten.

Chloroquine

Er was één studie die de duur van ziekenhuisopname, opklaring van symptomen, bijwerkingen en virale klaring beschreef bij behandeling met en zonder chloroquine. Op basis van deze literatuur kan geen conclusie worden getrokken (overall bewijskracht zeer laag). Mortaliteit en respiratoire ondersteuning werden niet beschreven. Omdat er geen bewijs is voor klinische effectiviteit van hydroxychloroquine voor COVID-19, is er van het verwante molecuul chloroquine ook geen klinische effectiviteit te verwachten.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

In de verschillende studies werd er geen klinisch relevant effect gevonden bij patiënten die hydroxychloroquine kregen ten opzichte van de controle groepen. Wel werd er voor mortaliteit een klein (niet klinisch relevant) voordeel gevonden voor de controle groep binnen de patiëntengroep die was opgenomen in het ziekenhuis. Daarnaast kan het gebruik van hydroxychloroquine wel mogelijk gepaard gaan met ernstige bijwerkingen bij patiënten, zoals cardiotoxiciteit.

Kosten (middelenbeslag)

Gezien het gebrek aan effectiviteit wordt hydroxychloroquine niet (meer) voorgeschreven aan patiënten met COVID-19.

Aanvaardbaarheid, haalbaarheid en implementatie

Hydroxychloroquine wordt niet (meer) voorgeschreven bij de behandeling van COVID-19, dus de werkgroep voorziet geen problemen qua implementatie. Wel kan het zijn dat sommige patiënten nog denken dat hydroxychloroquine of chloroquine werkzaam is tegen COVID-19. Goede voorlichting is hierbij belangrijk om de aanvaardbaarheid bij deze patiënten te vergroten.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

In de verschillende studies werd er geen klinisch effect gevonden bij patiënten die hydroxychloroquine kregen ten opzichte van de controlegroepen. Daarentegen kan het gebruik van hydroxychloroquine wel mogelijk gepaard gaan met (klinisch relevantie) bijwerkingen en mogelijk een kleine toename van de mortaliteit. Op basis hiervan kan geconcludeerd worden dat hydroxychloroquine geen plaats heeft bij de behandeling van COVID-19.

Onderbouwing

Achtergrond

Hydroxychloroquine wordt toegepast bij de behandeling van uiteenlopende ziektebeelden, waaronder reumatoïde artritis, Q-koorts en Systemische Lupus erythematoses (SLE). Hydroxychloroquine heeft een gelijkende molecuulstructuur als chloroquine: aan chloroquine werd een hydroxyethylgroep toegevoegd om de cumulatieve toxiciteit te reduceren. Al vroeg in de pandemie, werd er van zowel hydroxychloroquine als chloroquine in vitro een antiviraal effect aangetoond (Liu, 2020; Wang, 2020), al was dit middels niet klinisch gevalideerde testsystemen. In de beginfase van de COVID-19 pandemie werd hydroxychloroquine gegeven aan patiënten met COVID-19. In een redelijk vroege fase wezen de eerste redelijk uitgevoerde observationele vergelijkende studies al op de afwezigheid van een klinisch relevant effect. Inmiddels is in diverse gerandomiseerde studies (RCT's) de effectiviteit van hydroxychloroquine onderzocht om de plaats van hydroxychloroquine bij de behandeling van COVID-19 patiënten te bepalen.

Conclusies / Summary of Findings

Hydroxychloroquine in hospitalized COVID-19 patients

Mortality (crucial)

Moderate GRADE	Treatment with hydroxychloroquine probably results in little to no difference in mortality compared with treatment without hydroxychloroquine in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2020; Chen, 2020; RECOVERY trial (Horby, 2020); Lyngbakken, 2020; SOLIDARITY trial (Pan, 2020); Self, 2020; Tang, 2020; Ulrich, 2020 (TEACH).</i>

Extensive respiratory support (crucial)

Moderate GRADE	Treatment with hydroxychloroquine probably results in little to no difference in need for extensive respiratory support compared with treatment without hydroxychloroquine in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2020; RECOVERY trial (Horby, 2020); SOLIDARITY trial (Pan, 2020); Ulrich, 2020 (TEACH).</i>

Duration of hospitalization (important)

Low GRADE	Treatment with hydroxychloroquine may result in little to no difference in length of stay compared with treatment without hydroxychloroquine in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2020; RECOVERY trial (Horby, 2020); Pan, 2020; Self, 2020; Ulrich, 2020 (TEACH).</i>

Time to clinical improvement (important)

Very low GRADE	The evidence is uncertain about the effect of treatment with hydroxychloroquine on time to clinical improvement compared to treatment without hydroxychloroquine in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2020; Chen, 2020; Lyngbakken, 2020; Self, 2020; Tang, 2002; Ulrich, 2020 (TEACH).</i>

Hydroxychloroquine in non-hospitalized COVID-19 patients

Mortality (crucial)

Low GRADE	Treatment with hydroxychloroquine may result in little to no difference in mortality compared with treatment without hydroxychloroquine in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Mitjà, 2020; Omrani, 2020 (Q-PROTECT); Skipper, 2020</i>

Hospitalization (important)

Very low GRADE	The evidence is uncertain about the effect of treatment with hydroxychloroquine on risk of hospitalization compared to treatment without hydroxychloroquine in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Mitjà, 2020; Skipper, 2020</i>

Time to clinical improvement (important)

Very low GRADE	The evidence is uncertain about the effect of treatment with hydroxychloroquine on time to clinical improvement compared to treatment without hydroxychloroquine in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Mitjà, 2020; Omrani, 2020 (Q-PROTECT); Skipper, 2020</i>

Samenvatting literatuur

Hydroxychloroquine in hospitalized COVID-19 patients

Eight RCTs investigated hydroxychloroquine in hospitalized patients (Abd-Elsalam, 2020; Chen, 2020; RECOVERY trial (Horby, 2020); Lyngbakken, 2020; SOLIDARITY trial (Pan, 2020)); Self, 2020; Tang, 2020; Ulrich, 2020 (TEACH)). An overview of the included RCTs is provided in Table 1.

Abd-Elsalam (2020) described a multicenter randomized controlled trial. Abd-Elsalam (2020) evaluated the efficacy and safety of hydroxychloroquine in addition to standard of care versus standard of care alone in patients with COVID-19. The study included hospitalized patients with suspected and confirmed COVID-19. Patients were stratified in mild, moderate, and severe disease according to the WHO interim guidelines. Mild cases represented patients with uncomplicated upper respiratory tract viral infection. Moderate cases represented patients with pneumonia but without need for supplemental oxygen. Severe cases represented cases with fever or suspected respiratory infection, respiratory rate >30 breath/min, severe respiratory distress, or SpO₂ 93% on room air. The intervention group (n=97) received 400 mg hydroxychloroquine twice per day (on day one) followed by 200 mg tablets twice per day added to the standard of care for 15 days. The control group (n=97) received standard of care only. Standard of care consisted of paracetamol, oxygen, fluids (according to assessment), empiric antibiotic (cephalosporins), oseltamivir if needed (75 mg/12 hours for 5 days), and invasive mechanical ventilation with hydrocortisone for severe cases if PaO₂ < 60 mmHg, O₂ saturation < 90% despite oxygen or non-invasive ventilation, progressive hypercapnia, respiratory acidosis (pH < 7.3), and progressive or refractory septic shock. The length of follow-up was four weeks. The following relevant outcome measures were included: mortality, respiratory support (mechanical ventilation/Optiflow), duration of hospitalization, time to clinical improvement. The primary outcomes were recovery within 28 days, need for mechanical ventilation, or death. There were no difference between the two groups regarding the primary outcomes.

Chen (2020) described an open-label randomized clinical trial. Chen (2020) evaluated the efficacy and tolerability of hydroxychloroquine in adult hospitalized patients with mild to moderate COVID-19 disease. The study included patients aged between 20 and 79 years and confirmed positive for SARS-CoV-2 infection by RT-PCR. Patients in the intervention group (n=21) received 400 mg hydroxychloroquine twice per day on day one and 200 mg twice per day for six days plus standard of care. The control group (n=12) received standard of care only. Standard of care consisted of supportive treatment without antibiotics for subjects with mild clinical COVID-19 symptoms and with antimicrobial therapy for subjects presenting with moderate clinical COVID-19 symptoms. The antimicrobial treatment consisted of: (1) ceftriaxone two gram daily for seven days plus azithromycin 500 mg on the first day and 250 mg on days two to five; or (2) levofloxacin 750 mg daily for five days; or (3) levofloxacin 500 mg daily; or (4) moxifloxacin 400 mg daily for seven to 14 days for subjects allergic to ceftriaxone or azithromycin or according to physician discretion. The length of follow-up was 14

days. The following relevant outcome measures were included: time to clinical improvement. The primary endpoint was to evaluate the time to negative rRT-PCR assessments from randomization, up to 14 days. The study showed that HCQ failed the primary endpoint of shortening the viral clearance interval.

Horby (2020) (RECOVERY trial) described a randomized controlled open-label trial conducted in 176 National Health Service (NHS) hospitals in the UK. The RECOVERY trial (Horby, 2020) reported the results of a comparison between hydroxychloroquine and usual care involving patients hospitalized with COVID-19. The study included patients who had clinically-suspected or laboratory confirmed SARS-CoV-2 infection and no medical history that might put patients at substantial risk if they were to participate in the trial. Patients in the intervention group (n=1561) received hydroxychloroquine sulfate (in the form of a 200 mg tablet containing a 155-mg base equivalent) in a loading dose of four tablets (total dose, 800 mg) at baseline and at six hours, which was followed by two tablets (total dose, 400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next nine days or until discharge. The control group (n=3155) received standard of care only. The standard of care differed between hospitals but was not further described. At total of 288 (9.2%) patients received dexamethasone, 638 (20.3%) azithromycin or other macrolide, 84 (2.7%) tocilizumab or sarilumab, 6 (0.2%) Lopinavir-Ritonavir, 2 (0.1%) remdesivir, and 12 (0.4%) hydroxychloroquine. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, respiratory support (mechanical ventilation / optiflow), duration of hospitalization and cardiac-related events. The results . The primary outcome was 28-day mortality and occurred in 421 patients (27.0%) in the hydroxychloroquine group and in 790 (25.0%) in the usual-care group (rate ratio 1.09; 95% CI 0.97 to 1.23; P=0.15). These results suggested that patients in the hydroxychloroquine group were less likely to be discharged from the hospital alive within 28 days than those in the usual-care group

Lyngbakken (2020) described a single center two-arm open-label group-sequential pragmatic randomized controlled trial. Lyngbakken (2020) assessed the efficacy and safety of hydroxychloroquine therapy in addition to standard of care on SARS-CoV-2 oropharyngeal viral kinetics in hospitalized patients with moderately severe COVID-19. The study included patients. The intervention group (n=27) received 400 mg hydroxychloroquine sulfate twice per day for seven days in addition to standard of care. Standard care was similar for all

patients included in the study, and encompassed appropriate level and intensity of medical treatment according to local and national guidelines, but was not further described. The pharmacological treatment of the included patients was not described. The control group (n=26) received standard of care only. The length of follow-up was 30 days. The following relevant outcome measures were included: mortality, time to clinical improvement, respiratory support (non-invasive ventilation). The primary outcome was rate of decline in SARS-CoV-2 viral load in the oropharynx from baseline through the first 96 h after randomization. The estimated mean difference between groups was 0.27 (95% CI -0.92 to 1.47) log₁₀ RNA copies/mL at randomization, 0.06 (95% CI -1.15 to 1.26) log₁₀ RNA copies/mL at 48 h, and -0.16 (95% CI -1.67 to 1.36) log₁₀ RNA copies/mL at 96 h. These results suggested that treatment with hydroxychloroquine did not result in a significantly greater rate of decline in SARS-CoV-2 oropharyngeal viral load compared to standard care alone during the first five days.

Pan (2020) (SOLIDARITY trial) described an open-label randomized controlled trial. This trial compared the

efficacy of the addition of either hydroxychloroquine, remdesivir, lopinavir or interferon with or without lopinavir to standard of care in hospitalized patients with COVID-19. The study included patients who were aged 18 years or older, diagnosed with COVID-19, not known with receiving any trial drug, not expected to be transferred elsewhere within 72 hours, and had no contraindication to any trial drug. Regarding hydroxychloroquine, the intervention group (n=947) orally received four tablets hydroxychloroquine at hour 0, four tablets at hour six, and, starting at hour 12, two tablets twice daily for ten days in addition to local standard of care. Each tablet contained 200 mg of hydroxychloroquine sulfate (155 mg of hydroxychloroquine base per tablet). The control group (n=906) received local standard of care at a time and place in which that drug was locally available. Pharmacological treatment was not further specified. The length of follow-up was 28 days or up to discharge. The following relevant outcome measures were included: mortality, respiratory support (mechanical ventilation/Optiflow) and duration of hospitalization. The primary outcome was in-hospital mortality and occurred in 104 of 947 patients receiving hydroxychloroquine and in 84 of 906 receiving its control (rate ratio, 1.19; 95% CI, 0.89 to 1.59; P=0.23). Hydroxychloroquine had little to no effect on overall mortality.

Self (2020) described a double-blind randomized controlled trial. Self (2020) assessed whether hydroxychloroquine is an efficacious treatment for hospitalized adults with COVID-19. The study included adults aged 18 years or older who were hospitalized for less than 48 hours with laboratory-confirmed SARS-CoV-2 infection and symptoms of respiratory illness for less than ten days. The intervention group (n=242) received 400 mg of hydroxychloroquine sulfate in pill form twice per day for the first two doses and then 200 mg in pill form twice per day for the subsequent eight doses, for a total of ten doses over five days. The control group (n=237) received matching placebo in the same dosing frequency. Among the 479 patients in the trial, remdesivir, azithromycin, and corticosteroids were received by 104 (21.7%), 91 (19.0%), and 88 (18.4%) patients, respectively, during the same hospitalization in which they were enrolled in the trial. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement, respiratory support (non-invasive ventilation). The primary outcome was clinical status 14 days after randomization assessed with a 7-category ordinal scale (the COVID Outcomes Scale) recommended by the World Health Organization. At day 14 the difference in COVID Outcomes Scale score between the hydroxychloroquine group (median (IQR) score, 6 (4-7)) and placebo group (median (IQR) score, 6 (4-7)) with an adjusted OR of 1.02 (95% CI, 0.73 to 1.42). Treatment with hydroxychloroquine did not significantly improve clinical status at day 14 compared with placebo.

Tang (2020) described a multicenter open-label randomized controlled trial. Tang (2020) assessed the efficacy and safety of hydroxychloroquine plus standard of care compared with standard of care alone in hospitalized adults with mild, moderate and severe COVID-19. The study included patients aged 18 years or older, ongoing SARS-CoV-2 infection confirmed in upper or lower respiratory tract specimens with RT-PCR, willingness to participate, and consent not to be enrolled in other clinical trials during the study period. Patients in the intervention group (n=75) received hydroxychloroquine in addition to standard of care within 24 hours after randomization, with a loading dose of 1200 mg daily for three days followed by a maintenance dose of 800 mg daily for the remaining days. The total treatment duration was two weeks for patients with mild to moderate disease and three weeks for those with severe disease. The control group (n=75) received standard of care only. Standard of care was aligned with the indications from the updated national clinical practice guidelines for COVID-19 in China. Minimum requirements for the standard of care included the

provision of intravenous fluids, supplemental oxygen, regular laboratory testing, SARS-CoV-2 testing, hemodynamic monitoring, and intensive care, as well as the ability to deliver concomitant medications. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, time to clinical improvement. The primary outcomes for this trial were whether patients had negative conversion of SARS-CoV-2 by 28 days. The probability of negative conversion of SARS-CoV-2 among patients who were assigned to receive standard of care plus hydroxychloroquine by 28 days was 85.4% (95% CI: 73.8% to 93.8%) and 81.3% (71.2% to 89.6% in the standard care group. The difference in the probability of negative conversion between standard of care plus hydroxychloroquine and standard of care alone was 4.1% (95%CI: – 10.3% to 18.5%).

Administration of hydroxychloroquine did not result in a significantly higher probability of negative conversion than standard of care alone in patients admitted to hospital.

Ulrich (2020) described a multicenter double-blind randomized controlled trial. Ullrich (2020) evaluated the efficacy and safety of hydroxychloroquine in hospitalized patients with COVID-19. The study included hospitalized patients who had a positive SARS-CoV-2 RT-PCR within 72 hours of enrolment, at least one COVID-19 symptom, and written informed consent. The intervention group (n=67) orally received 400 mg (two tablets of 200 mg) of hydroxychloroquine sulfate twice per day on day one and 200 mg by mouth two times per day on days two to five. The control group (n=61) received a placebo tablet of 400 mg calcium citrate in the same regimen as the intervention group. Possible concomitant medications were antibacterial agents (23.4% azithromycin and 24.2% ceftriaxone), anticoagulation (53.9% VTE prophylaxis, 35.9% therapeutic anticoagulation and 29.7% antiplatelet agents), zinc (14.1%), corticosteroids (10.2%), tocilizumab (3.9%), lopinavir-ritonavir (0.8%), remdesivir (0.8%), convalescent plasma (13.3%), and clazakizumab (3.1%). The length of follow-up was 30 days. The following relevant outcome measures were included: mortality, respiratory support (mechanical ventilation / Optiflow), duration of hospitalization, time to clinical improvement, respiratory support (non-invasive ventilation). The primary outcome was a composite end point (death, intensive care unit admission, mechanical ventilation, extracorporeal membrane oxygenation, and/or vasopressor use) at day 14. At day 14, 11 (16.4%) subjects assigned to HCQ and 6 (9.8%, p=0.35) subjects assigned to placebo met the severe disease progression end point.

Treatment with hydroxychloroquine did not significantly improve clinical status at day 14 compared with placebo.

Table 1 Overview of RCTs comparing hydroxychloroquine with standard care in hospitalized COVID-19 patients.

Author	Disease severity, based on need for respiratory support*	Sample size	Dosage
Abd-El salam (2020)	Mild disease	I: N=97 C: N=97 Total: N=194	- 400 mg hydroxychloroquine twice per day (on day 1). - 200 mg tablets twice per day added to the standard of care for 15 days
Chen (2020)	Mild disease	I: N=21 C: N=12 Total: N=33	- 400 mg hydroxychloroquine twice per day on day 1. - 200 mg twice per day for six days.
Horby (2020) RECOVERY trial	Mixed: mild, moderate and severe disease If possible, sub group results are presented	I: N=1561 C: N=3155 Total: N=4716	- Four tablets of 200 mg hydroxychloroquine at baseline and at 6 hours. - Two tablets of 200 mg starting at 12 hours after initial dose and every 12 hours for the next nine days or until discharge.
Lyngbakken (2020)	Mixed: mild and moderate disease	I: N=27 C: N=26 Total: N=53	400 mg hydroxychloroquine sulfate 2 times daily for 7 days.
Pan (2020) SOLIDARITY trial	Mixed: mild, moderate and severe disease If possible, sub group results are presented	I: N=947 C: N=906 Total: N=1853	- 4 tablets of 200 mg hydroxychloroquine sulfate (155 mg of hydroxychloroquine base per tablet) at hour 0, 6 and 12. - 2 tablets twice daily for 10 days.
Self (2020)	Mixed: mild, moderate and severe disease	I: N=242 C: N=237 Total: N=479	- First 2 doses: 400 mg hydroxychloroquine in pill form 2 times daily. - 200 mg in pill form 2 times daily for the subsequent 8 doses, for a total of 10 doses over 5 days.
Tang (2020)	Mild disease	I: N=75 C: N=75 Total: N=150	1200 mg daily for three days followed by a maintenance dose of 800 mg daily for the remaining 11 days (mild to moderate patients) and 18 days (severe patients).
Ulrich (2020) TEACH trial	Mixed: mostly mild and moderate disease; 1.6% severe disease	I: N=67 C: N=61 Total: N=128	2 tablets of 200 mg hydroxychloroquine

*Disease severity categories:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen, CPAP, NIV, mechanical ventilation, ECMO).

N: Total sample size; I: Intervention; C: Control

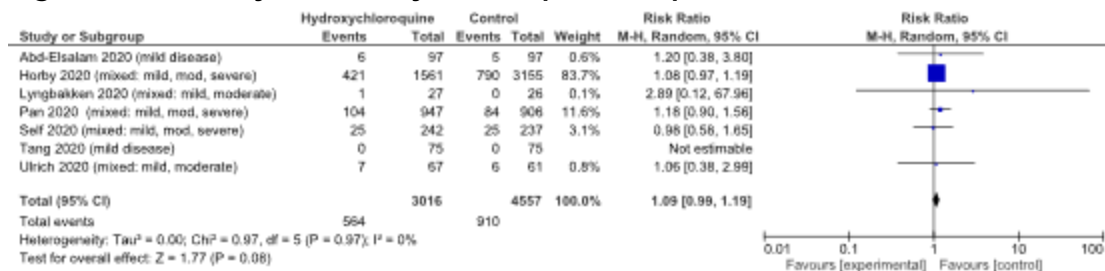
Results

Mortality (crucial)

Mortality, 28-30 days

The pooled incidence of mortality in hospitalized patients in the intervention group was 564/3016 (18.7%), compared to 910/4557 (20.0%) in the control group. Pooled risk ratio (RR) was 1.09 (95% CI 0.99 to 1.19; figure 1). The pooled risk difference (RD) was in favour of the control group (1.1%; 95% CI -0.3% to 2.5%). This is not a clinically relevant difference. The minor discrepancy between the crude and pooled numbers arises due to the weighing in the random-effects model. The RECOVERY trial (Horby, 2020) has the heaviest weight (83.7%) and is in favour of the control group (27.0% in the intervention group versus 25.0% in the control group).

Figure 1: Mortality (28-30 days) in hospitalized patients

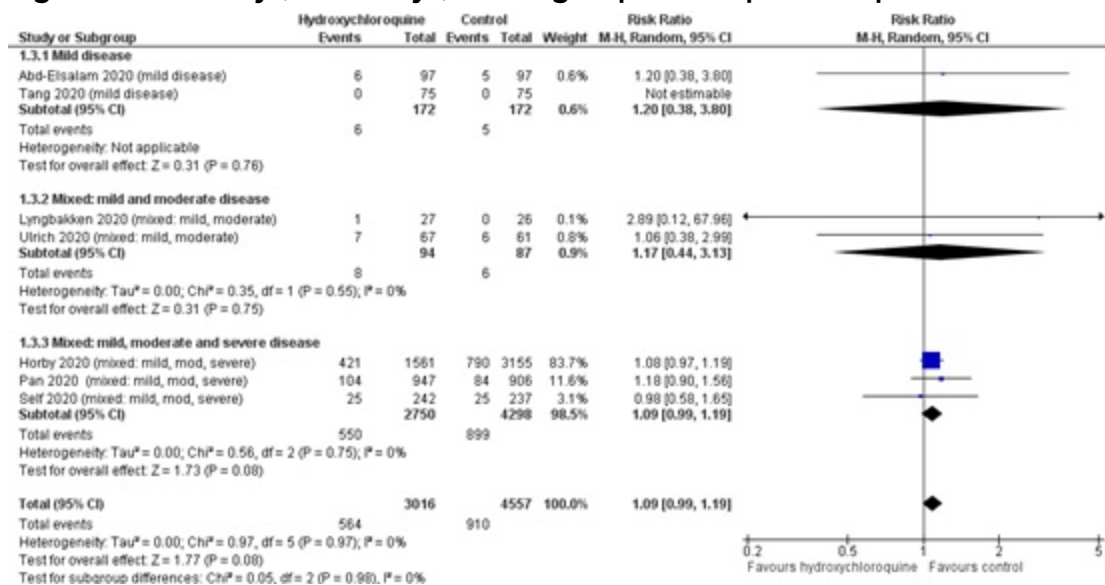


Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Mild disease

Abd-El salam (2020) and Tang (2020) reported data of patients with mild disease. The mortality rate was 6 of 172 (%) in the intervention group and 5 of 172 (%) in the control group, with a risk ratio of 1.20 (95% CI 0.38 to 3.80). As no events occurred in the study of Tang (2020), this risk ratio is based on the study results of Abd-El salam (2020).

Figure 2: Mortality (28-30 days) in sub-groups of hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Mild disease (not separately shown in meta-analysis)

In addition to the pooled results of Abd-Elsalam (2020) and Tang (2020) (figure 1), the RECOVERY trial (Horby, 2020) reported sub-group data of the patients that did not receive oxygen at baseline. The mortality rate was 58 of 362 (16.0%) in the intervention group and 99 of 750 (13.2%) in the control group.

Severe disease (not separately shown in meta-analysis)

The RECOVERY trial (Horby, 2020) reported subgroup data of the patients that received invasive mechanical ventilation at baseline. The mortality rate was 110 of 261 (42.1%) in the intervention group and 216 of 532 (40.6%) in the control group. The RR was 1.03 (95% CI 0.81 to 1.30).

The SOLIDARITY trial (Pan, 2020) reported subgroup data of the patients that received invasive mechanical ventilation at baseline. The HR for mortality was 1.26 (95% CI 0.76 to 2.10), in favour of the control group.

Mortality, other follow-up

Chen (2020) reported that no deaths took place in the intervention group (0/21) or control group (0/12) during the 14-day follow up.

Level of evidence of the literature

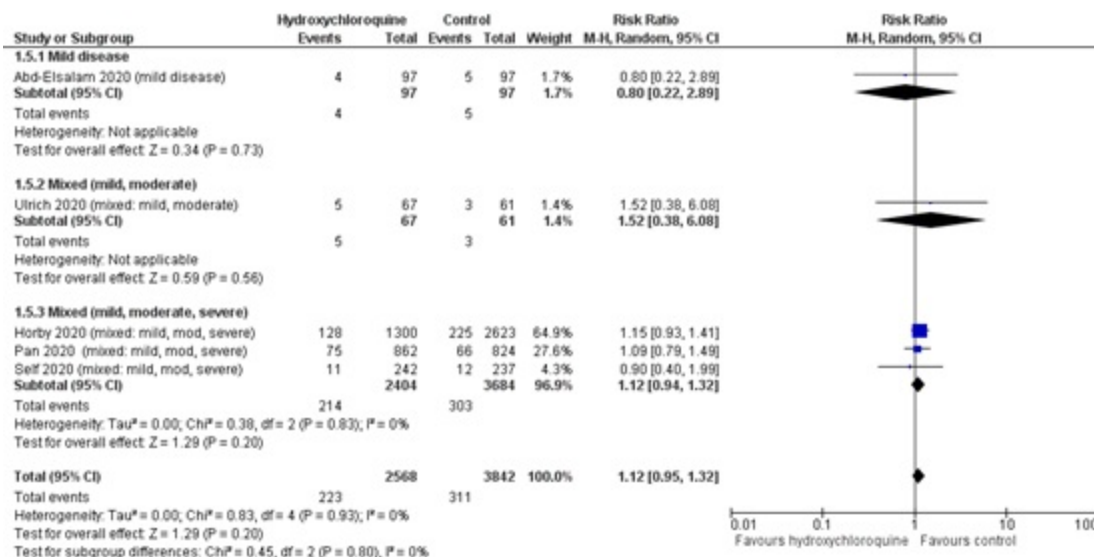
The level of evidence for hospitalized patients with COVID-19 started as high, because the studies were RCTs. The level of evidence was downgraded by one level because the confidence interval crosses both the threshold of no effect and the threshold of clinical relevance (imprecision, -1). The level of evidence for the outcome mortality in hospitalized patients is considered *moderate*.

Extensive respiratory support (crucial)

Extensive respiratory support in hospitalized patients with COVID-19 was reported in six studies (Abd-Elsalam, 2020; RECOVERY trial (Horby, 2020); Lyngbakken, 2020; SOLIDARITY trial (Pan, 2020) ; Self, 2020; Ulrich, 2020 (TEACH)).

The results were pooled in a meta-analysis (figure 3). The pooled incidence of mechanical ventilation in hospitalized patients in the intervention group was 212/2326 (9.1%) and 299/3605 (8.3%). The pooled RR was 1.12 (95% CI 0.95 to 1.32) and the pooled RD was 0.01 (95% CI -0.01 to 0.02) favouring the control group. This is not a clinically relevant difference.

Figure 3: Extensive respiratory support (28-30days) in hospitalized patients



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval

Mixed – mild & moderate disease

Lyngbakken (2020) reported by clinical status at day 14 that the none of patients requiring invasive mechanical ventilation or ECMO in the intervention group and 1 patient (4.0%) in the control group. One patient (3.8%) in de intervention group required non-invasive ventilation or high flow oxygen devices respectively versus 0 patients in the control group.

In addition, Ulrich (2020) reported by clinical status at day 14 that the percentage of patients requiring ventilator or ECMO was 3.0% ($n=2$) in the intervention group and 0% in the control group; requiring non-invasive ventilation or high flow oxygen devices respectively 10.4% ($n=7$) and 3.3% ($n=2$).

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by one level because of crossing the threshold for clinical relevance (imprecision, -1). The level of evidence for the outcome '*need for extensive respiratory support*', is considered *moderate*.

Duration of hospitalization (important)

Duration of hospitalization in hospitalized patients with COVID-19 was reported in five studies (Abd-Elisalam, 2020; RECOVERY trial (Horby, 2020); SOLIDARITY trial (Pan, 2020); Self, 2020; Ulrich, 2020 (TEACH)). Due to differences in reporting (mean, median or percentage), data were not pooled.

Mild disease

Abd-Elisalam (2020) reported that the mean (SD) duration of hospitalization was 11.04 (2.71) days in the intervention group ($n=97$), compared to 11.27 (2.19) days in the control group ($n=97$; MD -0.23 days; 95% CI -0.92 to 0.46)).

Mixed – mild & moderate disease

Ulrich (2020) found that the mean (SD) duration of hospitalization was 9.75 (10.3) days in the intervention group (n=67), compared to 6.80 (5.92) days in the control group (n=61). MD 2.95 days (95% CI 0.07 to 5.83), which was not considered as clinically relevant difference favouring the control group.

Mixed – mild, moderate & severe disease

The RECOVERY trial (Horby, 2020) reported that patients in the hydroxychloroquine group (n=1561) had a longer duration of hospitalization than those in the usual-care group (n=3155; median 16 days versus 13 days). In addition, the discharge rate at 28 days of follow-up was reported. In the intervention group, 931 of the 1561 (59.6%) patients were discharged, compared to 1983 of the 3155 (62.9%) patients in the control group (RR 0.90; 95% CI 0.83 to 0.98). This difference is considered as clinically relevant.

The SOLIDARITY trial (Pan, 2020) reported that the percentage of patients discharged from hospital at day 21 was 11.0% in the intervention group (n=947), compared to 10.0% in the control group (n=906), favouring the intervention group (RR 1.09; 95% CI 0.84 to 1.43). This difference is not considered as clinically relevant.

Self (2020) reported that the median number of hospital-free days through 28 days was 21 (IQR 11 to 24) in the intervention group and 20 (10 to 24) in the control group. The difference was 1 day (–1 to 3), which was not considered as clinically relevant difference.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of study limitations (lack of blinding, -1) and heterogeneity in reporting 'duration of hospitalization' and variance of point estimates across studies (inconsistency, -1). The level of evidence for the outcome 'duration of hospitalization' is considered *low*.

Time to clinical improvement (important)

Symptom resolution was reported in six studies for hospitalized patients with COVID-19 (Abd-Elsalam, 2020; Chen, 2020; Lyngbakken, 2020; Self, 2020; Tang, 2020; Ulrich, 2020 (TEACH)).

Mild disease

Abd-Elsalam (2020): The mean (SD) duration to clinical improvement (definition not described) was 9.43 (1.87) days in the intervention group compared to 9.52 (2.94) days in the control group (MD -0.09 days; 95% CI -0.78 to 0.60).

Chen (2020) reported that the incidence of resolution of symptoms* by day 14 was 28.6% (6/21) in the intervention group and 41.7% (5/12) in the control group. The RR was 0.69 (0.26 to 1.78), which is a clinically relevant difference favouring the control group.

Tang (2020) reported the time to alleviation of symptoms**. The median time was 19 days in the intervention group and 21 days in the control group (HR 1.01; 95% CI 0.59 to 1.74).

Mixed – mild & moderate disease

Lyngbakken (2020) reported the change in NEWS2-score from randomization to 96 hours. (higher score indicates worse condition). The mean change in the intervention group was 0.47

(95% CI -0.58 to 1.53) compared to 0.29 (95% CI -0.88 to 1.46) in the control group (MD in change score 0.18 (95% CI -1.40 to 1.76)).

Ulrich (2020) reported the number of fever-free days during the follow-up period of 30 days. The mean number of fever-free days was 6.40 (SD 0.94) in the intervention group and 6.31 (1.33) in the control group (MD 0.09).

Mixed – mild, moderate & severe disease

Self (2020) reported the time to recovery, defined as time to reach a clinical status of COVID Outcome Scale category 5, 6, or 7***. The median time to recovery was 5 (IQR 1 to 14) days in the intervention group and 6 (1 to 15) days in the control group.

** clinical recovery was defined as clinical recovery as the 1st time of three consecutive PCR tests and major symptoms showed negative results.*

*** defined as resolving from fever to an axillary temperature of 36.6°C or below, normalisation of SpO₂ (>94% on room air), and disappearance of respiratory symptoms including nasal congestion, cough, sore throat, sputum production, and shortness of breath.*

**** 5, hospitalized, not receiving supplemental oxygen; 6, not hospitalized and unable to perform normal activities; and 7, not hospitalized and able to perform normal activities)*

The definition of clinical improvement varied, and results were inconsistent between studies.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by three levels because of study limitations (lack of blinding, -1), heterogeneity in reporting 'clinical improvement' and variance of point estimates across studies (inconsistency, -1) and crossing thresholds for clinical relevance (imprecision, -1). The level of evidence for the outcome 'clinical improvement' is considered *very low*.

Description of studies: treatment with hydroxychloroquine in non-hospitalized COVID-19 patients

Three RCTs investigated hydroxychloroquine in non-hospitalized patients (Mitjà, 2020; Omrani, 2020 (Q-PROTECT); Skipper, 2020). An overview of the included RCTs is provided in Table 2.

Mitjà (2020) described an open-label randomized controlled trial. Mitjà (2020) aimed to determine whether early treatment with hydroxychloroquine would be more efficacious than no treatment for outpatients with mild COVID-19. The study included non-hospitalized patients aged 18 years or older with mild symptoms of COVID-19 for less than five days before enrollment, and with a positive PCR test for SARS-CoV-2. The intervention group (n=136) received 800 mg hydroxychloroquine – Dolquine on day one, followed by 400 mg once daily for six days. The control group (n=157) received no treatment aside from usual care. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement. The primary outcome was the reduction of viral RNA load in nasopharyngeal swabs at days 3, and 7 after treatment start. A mean reduction of viral load (-1.41 vs -1.41

$\log_{10}$ copies/mL in the control and intervention arm, respectively) was observed at day 3, which further declined at day 7 (-3.37 vs -3.44). No significant differences were found in the mean reduction of viral load (-0.07 (95%CI: -0.44 to 0.29)).

Treatment with hydroxychloroquine did not result in a significantly greater rate of decline in SARS-CoV-2 oropharyngeal viral load compared to standard care alone during the first five days.

Omrani (2020) described a parallel randomized controlled trial. Omrani (2020) determined whether use of hydroxychloroquine or hydroxychloroquine plus azithromycin was associated with higher rates of viral clearance compared to placebo. The study included non-hospitalized patients who had a positive SARS-CoV-2 PCR-test with mild or COVID-19 symptoms, respiration >29 /minute, or pulse oximetry on room air $<93\%$. The intervention group (hydroxychloroquine only, $n=152$) received 200 mg of hydroxychloroquine three times a day during seven days. In addition, two placebo tablets for azithromycin will be taken on day one and one on days two to five. The control group ($n=152$) received placebo tablets for hydroxychloroquine and placebo tablets for azithromycin and followed the same regimen as the intervention groups. The length of follow-up was 21 days. The following relevant outcome measures were included: mortality, time to clinical improvement. The study's primary outcome was achievement of virologic cure (PCR-negative status) as assessed on day six. At day six, 16 (10.5%) subjects assigned to the hydroxychloroquine + azithromycin group, 19 (12.8%) subjects assigned to the hydroxychloroquine group achieved virological cure and 18 (12.2%) in the placebo group achieved virological cure. No difference was found in groups' proportions achieving virologic cure at day six ($p=0.821$). Treatment with hydroxychloroquine (with or without azithromycin) did not result in a greater rate of virological cure after six days of treatment.

Skipper (2020) described a randomized double-blind placebo controlled trial. Skipper (2020) investigated whether hydroxychloroquine could reduce COVID-19 severity in adult outpatients. The study included non-hospitalized adults who were required to have four or fewer days of symptoms and either PCR-confirmed SARS-CoV-2 infection or compatible symptoms after a high-risk exposure to a person with PCR-confirmed COVID-19 within the past 14 days. The intervention group ($n=212$) received 800 mg (four tablets) once, then 600 mg (three tablets) six to eight hours later, then 600 mg (three tablets) once daily for four more days (five days in total). The control group ($n=211$) received placebo tablets of 400 mcg folic acid as an identical regimen as the intervention group. The length of follow-up was 14 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement. The primary outcome was change in overall symptom severity over 14 days.

Change in symptom severity over 14 days did not differ between the hydroxychloroquine and placebo groups (difference in symptom severity: relative, 12%; absolute, -0.27 point (95% CI, -0.61 to 0.07 point); $P=0.117$). At 14 days, 49 subjects (24%) receiving hydroxychloroquine had ongoing symptoms compared with 59 (30%) receiving placebo ($P=0.21$). Treatment with hydroxychloroquine did not substantially reduce symptom severity.

Table 2. Overview of RCTs comparing hydroxychloroquine with standard care in non-hospitalized COVID-19 patients.

Author	Disease severity	Sample size	Dosage
Mitjà (2020)	Mild	I: N=136 C: N=157 Total: N=293	800 mg hydroxychloroquine – Dolquine on day one. - 400 mg once daily for 6 days.
Omrani (2020)	Mild or no symptoms included	I: N=152 C: N=152 Total: N= 304	200 mg of hydroxychloroquine 3 times per day for 7 days.
Skipper (2020)	Mild	I: N=212 C: N=211 Total: 423	- 800 mg (four tablets) once. - 600 mg (three tablets) 6 to 8 hours later. - 600 mg (three tablets) once daily for 4 more days (5 days in total).

Results

Mortality (crucial)

Mortality was reported in three studies (Mitjà, 2020; Omrani, 2020 (Q-PROTECT); Skipper, 2020).

Mortality, 28-30 days

Mitjà (2020) reported no deaths among all participants up to 28-days of follow up.

Other

Omrani (2020) reported no deaths among all study participants up to 21 days of follow-up.

Skipper (2020) reported 1 death in the intervention group and 1 death in the control group after 14 days.

Level of evidence of the literature

The level of evidence for non-hospitalized patients with COVID-19 started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of the small number of participants and the small number of events in the studies (imprecision, -2). The level of evidence for the outcome mortality in non-hospitalized patients is considered *low*.

Hospitalization (important)

Two studies reported the incidence of hospitalization. Mitja (2020) reported that 8 of the 136 (5.9%) patients in the intervention group needed hospitalization in the 28-day follow-up period, compared to 11 of the 157 (7.0%) patients in the control group (RR 0.84; 95% CI 0.35 to 2.03).

Skipper reported hospitalization in the 18-day follow-up period for 4 of the 212 (1.9%) patients in the intervention group and 10 of the 211 (4.7%) patients in the control group. Two of the hospitalizations in the control group were reported not being related to the study (RR 0.40; 95% CI 0.13 to 1.25).

Level of evidence

The level of evidence for non-hospitalized patients with COVID-19 started as high, because the studies were

RCTs. The level of evidence was downgraded by three levels because of study limitations (risk of bias, -1), the small number of participants and the small number of events in the studies and crossing both thresholds for clinical relevance (imprecision, -2). The level of evidence for the outcome mortality in non-hospitalized patients is considered *very low*.

Time to clinical improvement (important)

Clinical improvement was reported in three studies (Mitjà, 2020; Omrani, 2020 (Q-PROTECT); Skipper, 2020).

Mitjà (2020) reported a median (IQR) time to complete symptom resolution* of 10.0 (4 to 18) days in the intervention group and 12.0 (6 to 21) days in the control group. The difference was two days, not a clinically relevant difference in favour of the intervention group.

Omrani (2020) reported the number of patients that were symptomatic at day one and asymptomatic at day 7, 14 and 21. Of patients in the first intervention group, respectively 80.0%, 95.7% and 97.1% was asymptomatic at those follow-up moments, compared to 79.9%, 92.8% and 98.6% in the second intervention group and 88.1%, 96.7% and 93.3% in the control group.

Skipper (2020) reported change in symptom severity score based on the Visual Analog Scale (VAS)** from baseline to 14 days. The change in symptom severity score in the intervention group was -2.60 points (SE 0.12), compared to -2.33 (SE 0.12) in the control group. Absolute difference -0.27 (95% CI -0.61 to 0.07), which is not a clinically relevant difference.

**Time to complete resolution of symptoms was defined as median time from randomization to the resolution of COVID-19 symptoms. Resolution of symptoms was assessed sequentially using a symptoms questionnaire designed to gather information on the type of symptom and last day experienced; complete resolution was considered when no COVID-19-related symptoms were reported at all.*

***Overall symptom severity was collected via a digital slider bar, which was marked with "0=no symptoms"; 5 (placed in the middle); and "10=severe symptoms".*

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by three levels because of study limitations (risk of bias, -1), heterogeneity in reporting 'clinical improvement' (inconsistency, -1) and small number of participants (imprecision, -1). The level of evidence for the outcome 'time to clinical improvement' is considered *very low*.

Non-invasive respiratory support (important)

Respiratory support was not reported for non-hospitalized patients with COVID-19.

Level of evidence of the literature

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Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with hydroxychloroquine compared to treatment without hydroxychloroquine in patients with COVID-19?

PICO 1

P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
I: hydroxychloroquine + standard care
C: standard care only / placebo treatment + standard care
O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

P: non-hospitalized patients with COVID-19
I: hydroxychloroquine + standard care
C: standard care only / placebo treatment + standard care
O: 28-30 day mortality (if not available, any other reports of mortality), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization, and time to clinical improvement were considered as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS). Non-invasive respiratory support was defined as supplemental oxygen low flow oxygen or non-rebreathing mask.

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and hospital admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow],

continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 7 January 2021. The detailed search strategy is outlined under Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in an indexed journal, comparing treatment with hydroxychloroquine and standard care to standard care alone or treatment hydroxychloroquine and standard care to placebo and standard care in patients with COVID-19.

The systematic literature search resulted in 33807 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials. Eventually, eleven studies were included.

An additional search was performed until 2 September 2021 resulting in 77600 hits. Important study characteristics and results were summarized in the evidence tables. Ten additional studies were included. The assessment of the risk of bias is summarized in the additional risk of bias tables. None of the additional RCTs found a clinical benefit in favour of hydroxychloroquine. Since the new available studies did not change the recommendations, the literature summary was not updated.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, eleven RCTs were included in the analysis of the literature. Eight studies investigated hydroxychloroquine in hospitalized patients (see Table 1). Three studies investigated hydroxychloroquine in non-hospitalized patients (see Table 2). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Remdesivir

Uitgangsvraag

Wat is de plaats van remdesivir bij de behandeling van COVID-19 patiënten?

Aanbeveling

Remdesivir wordt niet aanbevolen als standaardbehandeling van opgenomen patiënten met COVID-19

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder remdesivir bij patiënten met COVID-19. Tot 17 oktober 2021 werden er 6 gerandomiseerde gecontroleerde studies (RCTs) gevonden met in totaal 4289 patiënten in de remdesivir-groep en 3925 in de controle-groep. Een zevende studie (Barratt-Due, 2021) rapporteerde data van een subgroep van Noorse patiënten uit de Solidarity trial (Pan, 2020). In deze studie werd nieuwe data gepubliceerd over de mogelijke antivirale effecten van remdesivir en er werd gedetailleerde klinisch informatie beschreven. De studie van Barratt-Due werd daarom alleen meegenomen bij de evaluatie van specifieke subgroepen.

Omdat de geïnccludeerde studies heterogene patiëntgroepen bevatten, zijn de resultaten, waar mogelijk, opgesplitst voor patiënten met milde, matige en ernstige COVID-19 symptomen op basis van respiratoire ondersteuning bij inclusie. Er werden alleen RCTs geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat er vijf ongeblindeerde of open-label trials waren, met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten, werd de kwaliteit van dit bewijs naar beneden bijgesteld. Daarnaast waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. Eventueel werd de kwaliteit van het bewijs naar beneden bijgesteld als er veel heterogeniteit tussen de studies was, bijvoorbeeld in rapportage van de uitkomstmaat. De geïnccludeerde patiënten verschilden ook per studie (bijvoorbeeld in de ernst van ziekte bij inclusie). Deze verschillen in inclusie werden niet meegenomen in de gradering van de studies, maar zullen wel worden meegenomen in de overwegingen.

Mortaliteit

Op basis van de gevonden resultaten kan worden geconcludeerd dat er voor de cruciale uitkomstmaat 'mortaliteit', geen voordeel is voor behandeling van opgenomen patiënten met remdesivir (risicoverschil: 0.01, 95%CI -0.01 tot 0.02; relatief risico 0.93, 95% CI 0.74-1.16). Dit is gebaseerd op 6 studies en heeft bewijskracht *moderate*.

In de studie van Beigel (2020) werd er wel een voordeel gezien van remdesivir op de mortaliteit na 28-29 dagen in de mensen met matig ernstige ziekte (patiënten met alleen extra zuurstof bij opname, maar geen vorm van invasieve beademing; ziekte ernst 'moderate' in Figuur 2). De studie van Ader (2021) en Pan (2020) bevestigden deze bevinding niet. Na het poolen en wegen van de data van de drie studies waren deze resultaten niet statistisch significant (risicoverschil: 3%, 95%CI -1% tot 7% en relatief risico 0.69, 95%CI 0.38 tot 1.23). De studie van Wang (2020) beschrijft geen specifieke subgroepen, maar ruim 80% van de populatie

bestond uit patiënten die nog niet ernstig zuurstofbehoefstig waren (wel zuurstoftoediening, maar geen invasieve beademing). In deze studie werd er ook geen voordeel van remdesivir gezien op de mortaliteit. Patiënten in deze studie werden wel relatief laat behandeld: na gemiddeld 10 dagen klachten. In subgroep analyses bij patiënten met een (matig) ernstige COVID-19 infectie werd er ook geen statistisch significant mortaliteitsverschil aangetoond in de verschillende studies.

De publicatie van Pan (2020) was een interim analyse van de Solidarity trial. In mei 2022 verscheen de publicatie waarin de eindresultaten gepubliceerd werden (WHO Solidarity Trial Consortium, 2022). Ook in deze analyse werd er voor opgenomen patiënten met COVID-19 (milde, matige en ernstige COVID-19 samengenomen) geen voordeel gezien van behandeling met remdesivir. Echter, bij een subgroep analyse van patiënten met alleen extra zuurstofbehoefte maar geen noodzaak tot invasieve beademing was er wel een klein voordeel bij analyse van de mortaliteit in het ziekenhuis (14,6% overleed in de groep met remdesivir ten opzichte van 16,3% in de controlegroep; RR 0,87 95% CI 0,76-0,99). Er werd ook een klein en niet statistisch significant voordeel op de mortaliteit in de groep patiënten die zonder extra zuurstofbehoefte werd opgenomen in het ziekenhuis (2,9% overleed in de groep met remdesivir ten opzichte van 3,8% in de controlegroep; RR 0,76 95% CI 0,46-1,28. De mogelijke voordelen van remdesivir die in deze eindresultaten beschreven worden zijn klein. Omdat dit verschil minder was dan de vooraf gedefinieerde grens van klinische relevantie (3% punten verschil), wijzigt dit resultaat niet onze conclusie. Een publicatie van Ali (2022) beschrijft ook een mogelijk lagere mortaliteit bij opgenomen patiënten met COVID-19 na behandeling met remdesivir. Dit verschil was niet statistisch significant. Omdat een groot deel van deze patiënten reeds beschreven werd in de Solidarity trial, verandert ook deze studie onze conclusie niet.

Overige uitkomstmaten

De gevonden studies tonen geen consistent positief klinisch effect van remdesivir op duur van ziekenhuisopname of andere uitkomstmaten, bewijskracht *laag*.

Wel liet de studie van Beigel (2020) zien dat de kans op het starten van beademing of andere vormen van invasieve respiratoire ondersteuning lager was in de remdesivir groep vergeleken met placebo. Ook toonde deze studie een significant sneller klinisch herstel en een kortere opnameduur van 5 dagen in het voordeel van remdesivir. Een voordeel dat ook bij een kleine RCT uit Egypte werd gezien: mediaan 10 dagen bij remdesivir en 16 dagen bij de standaard behandeling (Abd-El Salam, 2021). Deze RCT is gepubliceerd na het voltooiën van het literatuuronderzoek en inmiddels alweer teruggetrokken door het tijdschrift (Abd-El Salam S. Retraction Notice, 2022). Alle andere studies lieten een dergelijk voordeel niet consistent zien. Een subgroep analyse van de studie van Spinner (2020) bij mensen nog vroeg in het beloop van de ziekte, werd dit positieve effect ook niet gezien: geen statistisch significante kans op een verbetering van de kliniek gezien bij behandeling binnen 9 dagen na ontstaan van symptomen.

Antivirale werking

In vitro en op basis van dieronderzoek waren er aanwijzingen voor een antiviraal effect van remdesivir bij COVID-19. Echter, dit effect werd in een drietal klinisch studies niet aangetoond. De meeste data over effecten op de virale load is afkomstig uit de DisCoVeRy studie (Ader, 2021), waarin bij 677 patiënten op enig moment in hun ziektebeloop een of meerdere nasofarynx monsters werden afgenomen. Behandeling met remdesivir liet ten opzichte van standaard zorg geen verschil zien in daling van de mediane virale load van dag 0 tot dag 3, en ook verder in het beloop (na 15 en 29 dagen) werden er geen verschillen in virale load

waargenomen. Subgroep analyses van patiënten vroeg in hun ziektebeloop of met milde of matige ziekte lieten ook geen klinisch relevant antiviraal effect zien. De kleinere studie van Barratt-Due (2021) (n=36 met remdesivir en n=53 met standaardbehandeling) toonde ook geen significante daling in viral load in nasopharynx swabs in eerste 15 dagen na randomisatie (daily viral decrease rate 0.113; 95% CI -0.001-0.227). En Wang (2020) liet ook geen significant verschil zien in de afname van de viral load in de nasopharynx of oropharynx.

Conclusie

Uit de geïncludeerde RCTs blijkt dat er geen klinisch relevant verschil te zien is in de mortaliteit van opgenomen patiënten. De eindresultaten van de Solidarity trial (WHO Solidarity Trial Consortium, 2022) veranderen deze conclusie niet. Bij andere eindpunten (met name opnameduur) zijn er wel verschillen te zien met mogelijke klinische relevantie die door de toediening van remdesivir verklaard zouden kunnen worden. Klinische verbetering lijkt vooral sneller op te treden indien behandeling gestart wordt binnen 10 dagen na aanvang van symptomen bij patiënten met extra zuurstofbehoefte maar zonder indicatie voor (non)invasieve beademing. Deze voordelen worden met name in 1 studie waargenomen (Beigel, 2020). Deze studie werd verricht in een periode waarin corticosteroïd gebruik niet standaard gegeven werd. Of er een aanvullend effect aanwezig is, boven op de huidige standaard behandeling die nu corticosteroïden bevat, is hierdoor onduidelijk. Informatie uit de studie van Wang (2020), Ader (2021) en Barrett-Due (2021) tonen daarnaast geen klinisch relevante antivirale werking aan bij patiënten met zuurstofbehoefte. Het ontbreken van een effect op de virale klaring ontkracht het werkingsmechanisme van remdesivir. Alle bovenstaande redenen bijeengenomen maken dat er geen plaats meer is voor remdesivir in de standaard zorg van patiënten met COVID-19 in Nederland.

Overige overwegingen

In de context

Ook een Cochrane review trekt deze zelfde conclusie en stelt dat er matig-sterk bewijs is dat remdesivir een klein of geen effect heeft op de mortaliteit na 28 dagen (Ansems, 2021). Een mogelijk positief effect van remdesivir bij mensen met een beperkte zuurstofbehoefte wordt wel benoemd. In deze Cochrane review is de DisCoVeRy studie (Ader, 2021) nog niet meegenomen.

De WHO raadt in december 2021 - in tegenstelling tot de IDSA - het gebruik van remdesivir af bij opgenomen patiënten met COVID-19 in alle ziektestadia buiten studieverband ('weak or conditional recommendation against the use of remdesivir in hospitalised patients with COVID-19'). Dit is een zwakke/voorwaardelijke aanbeveling. Er is daarbij gebruik gemaakt van precies dezelfde gepubliceerde data die in deze richtlijn ook zijn gebruikt, met uitzondering van de DisCoVeRy studie die later is verschenen.

De IDSA richtlijn adviseert in december 2021 behandeling met remdesivir nog wel bij patiënten met zuurstofbehoefte zonder mechanische ventilatie. Ook in dit advies is de meest recente DisCoVeRy studie nog niet meegenomen.

Bijwerkingen

Veiligheidsdata uit fase 1-onderzoek zijn nog niet gepubliceerd, ondanks dat er meerdere fase-1 onderzoeken zijn verricht. Vooral ALAT en ASAT-stijging wordt genoemd als bijwerking in de SmPC

(<https://lci.rivm.nl/remdesivir>). De EMA onderzoekt sinds 2020 of er een verhoogd risico is op nefrotoxiciteit bij gebruik van remdesivir naar aanleiding van berichten hierover bij patiënten met COVID-19 die remdesivir toegediend kregen.

In meerdere studies werd veiligheidsdata verzameld (Spinner, Wang, Ader, Barratt-Due). De DisCoVeRy studie van Ader (2020) onderzocht de veiligheid van remdesivir in 824 patiënten, waarbij er een vergelijkbaar aantal bijwerkingen werd gezien in de remdesivir groep ten opzichte van de controlegroep (32% versus 31% graad 3 of 4 bijwerkingen). Ook voor ernstige bijwerkingen was dit aantal nagenoeg gelijk. De studies van Spinner en Wang bevestigden deze data en lieten niet significant meer bijwerkingen zien bij het gebruik van remdesivir. In de studie van Barratt-Due werden bijwerkingen bij 42 patiënten met remdesivir bijgehouden. In deze kleine groep werden wat meer bijwerkingen gezien bij remdesivir (38.5% versus 25.3%), deze waren met name respiratoir van aard.

Samenvattend lijkt het gebruik van remdesivir niet gepaard te gaan met veel bijwerkingen.

Andere patiëntengroepen

Ook bij patiënten die niet zijn opgenomen in het ziekenhuis is remdesivir onderzocht (Gottlieb, 2022). In een groep van 562 ambulante patiënten met een hoog risico op een ernstig beloop toonde intraveneus toegediend remdesivir een voordeel: de kans op opname of overlijden binnen 28 dagen was 0,7% in de remdesivir groep versus 5,3% in de controle groep (hazard ratio 0,13 (95% CI 0,03-0,59)). Remdesivir werd in deze studie gedurende 3 opeenvolgende dagen intraveneus toegediend. Dit beperkt de praktische toepasbaarheid. Dit middel wordt daarom op dit moment ook niet aanbevolen in de ambulante setting. Onderzoek naar andere toedieningsvormen van remdesivir wordt op dit moment verricht.

Of het klinisch relevante effect van remdesivir ook ontbreekt in specifieke patiëntengroepen, zoals patiënten met een verminderd afweersysteem of heel vroeg in het ziektebeloop, is niet onderzocht. Hierover kan dan ook geen advies gegeven worden.

Kosten (middelenbeslag)

Remdesivir wordt niet (meer) aanbevolen bij de behandeling van COVID-19, de kosten zullen hier daarom niet beschreven worden.

Aanvaardbaarheid, haalbaarheid en implementatie

Remdesivir wordt niet (meer) aanbevolen bij de behandeling van COVID-19, dus implementatie is niet van toepassing.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Er werd geen klinisch relevant effect gevonden bij opgenomen patiënten die remdesivir kregen ten opzichte van de controle groepen. De bijwerkingen zijn nog beperkt onderzocht. Omdat het middel niet (meer) wordt voorgeschreven in het kader van de standaardbehandeling van COVID-19, zijn er geen specifieke voorkeuren of waarden beschreven van patiënten.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Van behandeling van opgenomen patiënten met remdesivir is geen winst op harde eindpunten zoals mortaliteit aangetoond. Slechts in enkele studies wordt er op andere eindpunten of in subgroepen een

beperkt verschil gezien met mogelijk beperkte klinische relevantie in het voordeel van remdesivir. Hiertegenover staat de observatie van (mogelijke) bijwerkingen en kosten. Op basis hiervan kan geconcludeerd worden dat remdesivir geen plaats heeft bij de standaardbehandeling van COVID-19.

Onderbouwing

Achtergrond

Remdesivir (GS-5734) is een nucleoside-analoog (prodrug) met in vitro activiteit tegen verschillende RNA-virussen. Het werd eerder getest als antiviraal middel voor behandeling van Ebola infecties (Warren, 2016), maar bleek niet voldoende klinisch effectief. Remdesivir heeft bij in-vitro onderzoek met onder meer humane longcellijnen activiteit tegen verschillende coronavirussen, onder meer SARS-CoV-1 laten zien (Sheahan, 2017). Voor SARS-CoV-2 is in vitro (Vero E6; niercellijn afkomstig van groene meerapen) antivirale activiteit gezien (Wang M, 2020). In beide studies ligt de EC₅₀ bij lage micromolaire concentraties. Echter het is onduidelijk de of de gebruikte modellen en concentraties representatief zijn voor een infectie bij mensen in de longen. Tevens ontbreken validatie studies. Een studie met MERS-CoV infectie bij muizen lieten een antiviraal effect en minder orgaanschade van remdesivir zien (Sheahan, 2020). Toediening van remdesivir bij resusapen, 12 uur na blootstelling aan SARS-CoV-2, bleek te leiden tot minder longontsteking en een lagere hoeveelheid virus in de longen (Williamson, 2020).

Deze data leidden er toe dat remdesivir al vanaf het begin van de pandemie onderzocht werd voor behandeling van COVID-19. Echter zijn er nooit klinische dose-finding studies gedaan. Inmiddels is in diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit onderzocht om de plaats van remdesivir bij de behandeling van COVID-19 patiënten te bepalen.

Conclusies / Summary of Findings

Mortality (crucial)

Moderate GRADE	Treatment with remdesivir probably results in little to no difference in mortality when compared with treatment without remdesivir in <u>hospitalized</u> patients with COVID-19. <i>Sources: Ader, 2021; Beigel, 2020; Mahajan, 2021; Pan, 2020; Spinner, 2020; Wang, 2020</i>

Extensive respiratory support (crucial)

Low GRADE	Treatment with remdesivir may result in little to no difference in the need for extensive respiratory support when compared with treatment without remdesivir in <u>hospitalized</u> patients with COVID-19. <i>Sources: Barratt-Due, 2021; Beigel, 2020; Pan, 2020</i>

Duration of hospitalization (important)

Low GRADE	Treatment with remdesivir may result in little to no difference in the length of stay when compared with treatment without remdesivir in <u>hospitalized</u> patients with COVID-19. <i>Sources: Ader, 2021; Beigel, 2020; Pan, 2020; Wang, 2020</i>

Time to clinical improvement (important)

Low GRADE	Treatment with remdesivir may result in little to no difference in the time to clinical improvement when compared with treatment without remdesivir in <u>hospitalized</u> patients with COVID-19. <i>Sources: Ader, 2021; Beigel, 2020; Spinner, 2021; Wang, 2020</i>

Samenvatting literatuur

Ader (2021) (The DisCoVeRy trial) describes a phase 3, open-label, adaptive multicenter randomized controlled trial. This study evaluated the clinical efficacy of remdesivir in addition to standard of care versus standard of care alone in patients admitted to the hospital with COVID-19 with indication of oxygen or ventilation support. Standard of care included anticoagulants and corticosteroids as of a certain time point. Critically ill patients that required intensive care unit admission received 20 mg dexamethasone once daily for 5 days, followed by 10 mg once daily for 5 days at the clinician's discretion. In total, 40% of the patients received systemic corticosteroids and 7.5% corticosteroids via the inhaled route. Other supportive treatments, such as immunomodulatory agents were given at the investigator's discretion. None of the participants received a SARS-CoV-2 vaccine during the trial. The intervention group (n=429) received a remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) in addition to standard care. The control group (n=428) received standard of care alone. The length of follow-up was 29 days. The following relevant outcome measures were included: mortality, duration of hospitalization, clinical improvement. The primary outcome was the clinical status at day 15 measured by the WHO seven-point ordinal scale. The difference in clinical status at day 15 between the treatment groups was not statistically significant.

Barratt-Due (2021) (The NOR-Solidarity trial) described an open-label adaptive randomized controlled trial. This was an independent add-on randomized controlled trial to the WHO **Solidarity trial** (Pan, 2020). Barratt-Due (2021) evaluated the effects of remdesivir in hospitalized adult patients with confirmed COVID-19 infection. The 'disease severity' of the patients was not reported based on the requirement of respiratory support but on viral load. The intervention group (n=42) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) in addition to standard care. The control group (n=57) received standard of care alone. Standard of care changed during the study as a result of the recovery trial and updated WHO guidelines recommending systemic steroids for severe and critical COVID-19. In total, 2.4% of the patients in the intervention group received steroids, versus 1.8% in the control group. The length of follow-up was three months. The following relevant outcome measures were included: respiratory support. The primary outcome was in-hospital mortality. This outcome measure was also included in the WHO

Solidarity trial (Pan, 2020). In total, 7.1% (95%CI 1.8 to 17.5) of the patients in the intervention group died during hospitalization, versus 7.0% (95%CI 2.2 versus 15.6) in the control group. No significant differences were seen between the treatment groups in mortality during hospitalization.

Beigel (2020) (The Adaptive COVID-19 Treatment Trial (ACTT-1)) described a double-blind, multicenter randomized, placebo-controlled trial of intravenous remdesivir in adults who were hospitalized with COVID-19 and had evidence of lower respiratory tract infection. Most patients had either one (25.9%) or two or more (54.5%) of the prespecified coexisting conditions at enrolment, most commonly hypertension (50.2%), obesity (44.8%), and type 2 diabetes mellitus (30.3%). Of all patients, 903 (85.0%) were in the moderate-to-severe disease stratum (requiring invasive or non-invasive mechanical ventilation, or requiring supplemental oxygen, or an $\text{SpO}_2 \leq 94.0\%$ on room air, or tachypnea (respiratory rate ≥ 24 breaths per minute)) and 159 (15.0%) were categorized as having mild disease ($\text{SpO}_2 > 94.0\%$ and respiratory rate < 24 breaths per minute without supplemental oxygen requirement). The intervention group ($n=541$) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days). The control group ($n=521$) received placebo for up to 10 days. All patients received supportive care according to the standard of care for the trial site hospital. In total, the patients received a variety of concomitant treatments during the study course: 82.3% received antibiotics, 32.2% received vasopressors, 23.0% received corticosteroids, 7.5% received other anti-inflammatory medications (not specified), 4.8% received monoclonal antibodies targeting cytokines. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, respiratory support, duration of hospitalization, clinical improvement. The primary outcome was time to recovery, defined by either discharge from the hospital or hospitalization for infection-control purposes only. Those who received remdesivir had a significantly shorter median recovery time of 10 days, as compared with 15 days among those who received placebo.

Mahajan (2021) described a randomized controlled trial which evaluated the improvement in clinical outcomes with remdesivir treatment for five days in hospitalized patients who were between 18 and 60 years and had COVID-19 confirmed by PCR assay within the last 4 days. Patients on mechanical ventilation were excluded. The intervention group ($n=34$) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 4 additional days) plus the standard of care. The control group ($n=36$) received standard care alone. Drugs like corticosteroids and heparin were given as per standard care protocol (exact percentage not mentioned). Standard of care was not further specified in this study. The length of follow-up was 12 days or until discharge/death. The following relevant outcome measure was included: mortality. The primary outcome is the clinical status. Both groups had similar outcomes after adjustment for baseline clinical status.

Pan (2020) (The WHO Solidarity trial) described an open-label randomized controlled trial. Pan (2020) compared the efficacy of the addition of remdesivir to standard of care in hospitalized patients with COVID-19. The study included patients who were aged 18 years or older, diagnosed with COVID-19, not known with receiving any trial drug, not expected to be transferred elsewhere within 72 hours, and had no contraindication to any trial drug. The intervention group ($n=2743$) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days) in addition to standard care. The control group ($n=2708$) received local standard of care alone. In total, the patients received several concomitant drugs during the study course: corticosteroids (intervention group 47.8%, control group 47.6%), convalescent plasma (intervention group 1.9%, control group 2.1%), anti-IL-6 drug (intervention group 4.9%, control group

5.3%). The length of follow-up was 28 days or up to discharge. The following relevant outcome measures were included: mortality, respiratory support, and duration of hospitalization. The primary outcome was in-hospital mortality. Remdesivir did not reduce mortality, overall or in subgroup analyses.

Spinner (2020) describes a randomized open-label multicentre clinical trial of intravenous remdesivir in adults who were hospitalized with COVID-19. The intervention group (n=384) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily). Remdesivir was provided for either 5 days (intervention group 1, n=193) or 10 days (intervention group 2, n=191). The control group (n=200) received standard of care. Standard of care included steroids in 15-19% of the patients. The original protocol allowed use of other agents with presumptive activity against SARS-CoV-2 if such use was local standard care. This exception was disallowed in a subsequent amendment of the protocol. The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, clinical improvement. The primary outcome was clinical status on day 11 on a 7-point ordinal scale. On day 11, patients in the 5-day remdesivir group had statistically significantly higher odds of a better clinical status distribution than those receiving standard care. The clinical status distribution on day 11 between the 10-day remdesivir and standard care groups was not significantly different.

Wang (2020) describes a randomised, double-blind, placebo-controlled, multicentre trial of intravenous remdesivir in adults who were hospitalized with COVID-19. Almost all patients required a form of supplemental oxygen (supplemental oxygen, high-flow nasal cannula, non-invasive mechanical ventilation, ECMO or invasive mechanical ventilation) at day 1, except 3/78 (3.8%) of patients in the control group. The intervention group (n=158) received remdesivir (200 mg loading dose on day 1, followed by 100 mg daily for up to 9 additional days). The control group (n=78) received a placebo for up to 10 days. Patients received several concomitant drugs during the study course: corticosteroids (intervention group 65%, control group 68%), antibiotics (intervention group 90%, control group 94%), interferon alfa-2b (intervention group 29%, control group 38%), lopinavir-ritonavir (intervention group 28%, control group 29%), and vasopressors (intervention group 16%, control group 17%). The length of follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization, clinical improvement. The primary outcome was time to clinical improvement up to day 28, defined as the time (in days) from randomization to the point of a decline of two levels on a six-point ordinal scale of clinical status or discharged alive from hospital, whichever came first. Remdesivir was not associated with a difference in time to clinical improvement.

Table 1. Overview of RCTs comparing remdesivir with standard care in hospitalized COVID-19 patients.

Author	Disease severity, based on need for respiratory support*	Sample size	Dosage
Ader (2021)	Mixed: Mild: n=12 (1%) Moderate: n=492 (59%) Severe: n=326 (40%)	I: N=429 C: N=428 Total: N=857	- 200 mg remdesivir intravenously on day 1. - 100 mg once-daily (on days 2-10)

Barratt-Due (2021)	Mixed: Disease severity is defined based on viral load.	I: 42 C: 57 Total: 99	- 200 mg remdesivir intravenously (on day 0). - 100 mg once-daily (on days 1-9).
Beigel (2020)	Mixed: Mild: n=138 (13%) Moderate: n=435 (41%) Severe: n=478 (45%) Baseline score was missing in 1% of the patients).	I: 541 C: 521 Total: 1062	- 200 mg remdesivir intravenously (on day 1). - 100 mg once-daily (on days 2-10).
Mahajan (2021)	Mixed: Mild: 0 Moderate: n=53 (75.7%) Severe: n=17 (24.3%) mostly moderate receiving low flow supplemental oxygen (76%), severe cases received non-invasive ventilation or high-flow oxygen.	I: 34 C: 36 Total: 70	- 200 mg remdesivir intravenously (on day 1). - 100 mg once-daily (on days 2-5).
Pan (2020)	Mixed: Mild: n= 1325 (24.3%), moderate & severe: n= 4126 (75.7%)	I: N=2743 C: N=2708 Total: N=5451	- 200 mg remdesivir intravenously (on day 0). - 100 mg once-daily (on days 1-9).
Spinner (2020)	Mixed: Mild: n=491 (84%), Moderate: n=88 (15%) Severe: n=5 (1%)	I1 (5-day remdesivir): 193 I2 (10-day remdesivir): 191 C: 200 Total: N=584	- 200 mg remdesivir intravenously (on day 1). - 100 mg once-daily (on days 2-5 or 2-10).
Wang (2020)	Mixed: mild: n=3 (1%) moderate: n =194 (82%) severe: n=38 (16%) 1 patient in the remdesivir group died at day 1	I: N=158 C: N=78 Total: N=236	- 200 mg remdesivir intravenously (on day 1). - 100 mg once-daily (on days 2-10).

**Disease severity categories:*

- *mild disease (no supplemental oxygen);*
- *moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);*
- *severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS].*

N: Total sample size

I: Intervention

C: Control

Results

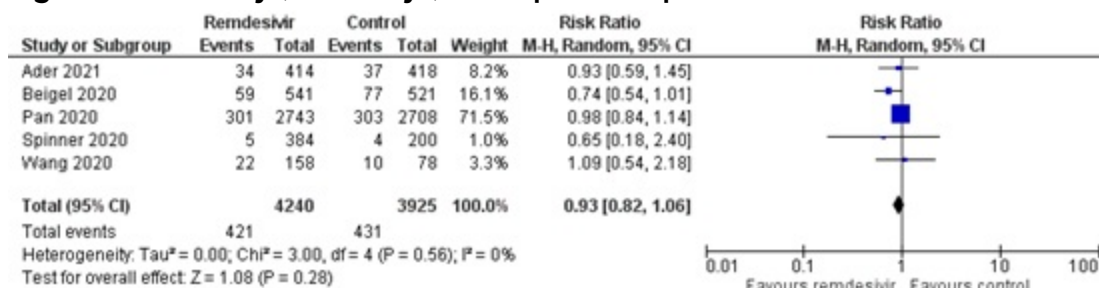
Mortality (crucial)

Mortality in hospitalized patients with COVID-19 was reported in six studies (Ader, 2021; Beigel, 2020; Mahajan, 2021; Pan, 2020; Spinner, 2020; Wang, 2020). The results are presented separately for a follow-up of 28-30 days and other length of follow-up. Barratt-Due (2020) reported mortality, however as these patients were already included in the WHO Solidarity trial (Pan, 2020). To prevent double representation, these results were not included in the meta-analysis.

Mortality, 28-30 days

The pooled incidence of mortality in hospitalized patients in the intervention group was 421/4240 (9.9%), compared to 431/3925 (11.0%) in the control group. The pooled RR was 0.93 (95% CI 0.82 to 1.06; Figure 1), in favour of the intervention group. The pooled RD was 0.01 (95%CI -0.01 to 0.02), in favour of the intervention group. This is not considered clinically relevant.

Figure 1: Mortality (28-30days) in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Subgroup analysis according to disease severity

Mild disease

Two studies reported the mortality specifically for patients with a mild disease severity (Beigel, 2020; Pan, 2020). The mortality was 14/736 (1.9%) in the intervention group, compared to 16/727 (2.3%) in the control group (Figure 2). The pooled RR was 0.85 (95% CI 0.42 to 1.72), in favour of the intervention group. The pooled RD was 0.00 (95% CI -0.02 to 0.01). This is not considered clinically relevant.

Moderate disease

Three studies reported the mortality for patients with a moderate disease severity (Ader, 2021; Beigel, 2020; Pan, 2020). The mortality in the intervention group was 216/2313 (9.3%), compared to 259/2265 (11.4%) in the control group (Figure 2). The RR was 0.69 (95%CI 0.38 to 1.23) in favour of the intervention group. The RD was just below 0.03 (95%CI -0.01 to 0.07), in favour of the intervention group. This is considered clinically relevant.

Severe disease

Two studies reported the mortality for patients with a severe disease severity (Ader, 2021; Beigel, 2020). The mortality was 164/641 (25.6%) in the intervention group, compared to 142/652 (21.8%) in the control group (Figure 2). The pooled RR was 1.16 (95% CI 0.96 to 1.41), in favour of the control group. The RD was 0.02 (95% CI -0.03 to 0.08). This is not considered clinically relevant.

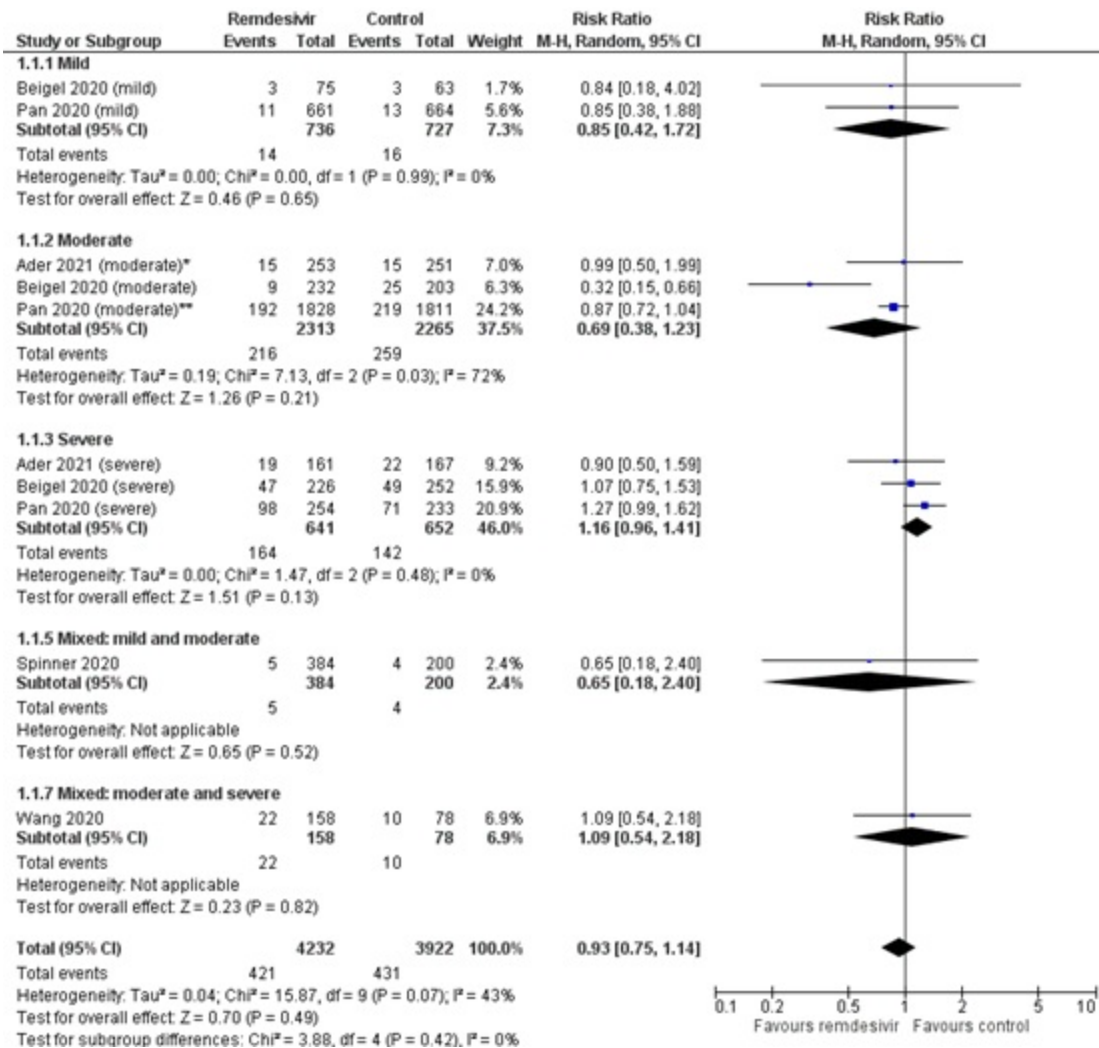
Mixed: mild & moderate disease

Spinner (2020) reported the mortality for patients with a mild and moderate disease severity. The mortality in the intervention group was 5/384 (1.3%), compared to 4/200 (2.0%) in the control group (Figure 2). The RR was 0.65 (95% CI 0.18 to 2.40) in favour of the intervention group. The RD was 0.01 (95% CI -0.02 to 0.03). This is not considered clinically relevant.

Mixed: moderate & severe disease

Wang (2020) reported the mortality for patients with a moderate and severe disease severity. The mortality in the intervention group was 22/158 (13.9%), compared to 10/78 (12.8%) in the control group (Figure 2). The RR was 1.09 (95% CI 0.54 to 2.18) in favour of the intervention group. The RD was 0.01 (95% CI -0.01 to 0.02). This is not considered clinically relevant.

Figure 2: Mortality (28-30days) in hospitalized patients by disease severity



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval.

*1% of the patients in the study of Ader (2021) had a mild disease severity. **Pan (2020) included patients who received high-flow oxygen in the moderate subgroup.

Mortality, other follow-up

Mahajan (2021) reported mortality during the 12-day follow up. The mortality was the 14.7% (5/34) in the intervention group, and 8.3% (3/36) in the control group (RR 1.76; 95%CI 0.46 to 6.82). The RD was 0.06 (95%CI -0.09 to 0.21), in favour of the control group. This means that patients in the intervention group have a higher risk of mortality. This is considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because there is a difference in effect estimates among the studies due to heterogeneity in study population (inconsistency, -1). The level of evidence for the outcome mortality in hospitalized patients is considered *moderate*.

Extensive respiratory support (crucial)

Initiation of mechanical respiratory support in hospitalized patients with COVID-19 was reported in two

studies (Beigel, 2020; Pan, 2020). The results were not pooled as only two studies could be included in the meta-analysis. Ader (2021) reported a combined outcome measure new mechanical ventilation, ECMO or death within 29 days and was therefore not included in the meta-analysis. Barratt-Due (2020) reported the initiation of mechanical respiratory support, however as these patients were already included in the WHO Solidarity trial (Pan, 2020), the results were not included in the meta-analysis.

Pan (2020) reported 295/2743 (10.8%) patients in the intervention group in whom respiratory support was initiated after randomization, compared to 284/2709 (10.5%) in the control group. This results in a RR of 1.03 (95% CI 0.88 to 1.20). The RD was 0.00 (95%CI -0.01 to 0.02). This means that there is no difference between the intervention and control group. Ventilation included invasive or non-invasive mechanical ventilation or extra-corporal membrane oxygenation.

Beigel (2020) reported that the number of patients that started non-invasive ventilation or high-flow oxygen during the study was 52/307 (16.9%) in the intervention group, compared to 64/266 (24.16%) in the placebo group. This results in a RR of 0.70 (95% CI 0.51 to 0.98), in favour of the intervention group. The RD was 0.07 (95%CI 0.00 to 0.14), in favour of the intervention group. This is considered clinically relevant. It is unclear whether these patients also started mechanical ventilation or ECMO during the study period.

Beigel (2020) also reported that the number of patients that started using mechanical ventilation or ECMO during the study was 52/402 (12.9%) in the intervention group, compared to 82/364 (22.5%) in the placebo group. This results in a RR of 0.57 (95% CI 0.42 to 0.79). The RD was 0.10 (95%CI 0.04 to 0.15), in favour of the intervention group. This is considered clinically relevant. It is unclear whether these patients also received non-invasive ventilation or high-flow oxygen before the start of mechanical ventilation or ECMO.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of heterogeneity in study results (inconsistency, -1) and because of a low number of events (imprecision, -1). The level of evidence for the outcome 'respiratory support' in hospitalized patients is considered *low*.

Duration of hospitalization (important)

Duration of hospitalization in hospitalized patients with COVID-19 was reported in three studies (Ader, 2021; Beigel, 2020; Wang, 2020). Due to differences in reporting, data were not pooled. Pan (2020) did not report the duration of hospitalization, but they rather reported the percentage at 7, 14 and 21 days. Therefore, the study was not included.

Ader (2021) reported that the median (IQR) number of days until hospital discharge within 29 days was 15 days (10 to 29) in the intervention group (n=253), compared to 13 days (8 to 29) in the control group (n=251). The difference was 2 days, this is not considered clinically relevant.

Beigel (2020) reported that the median (IQR) duration of initial hospitalization was 12 days (6 to 28) in the intervention group (n=541), compared to 17 days (8 to 28) in the control group. The median duration of initial hospitalization among those who did not die was 10 days (5 to 21) in the intervention group, and 14 days (7 to 27) in the control group. The difference is 5 or 4 days, which was both considered clinically relevant.

Wang (2020) reported that the median (IQR) duration of hospital stay was 25 days (16 to 38) in the intervention group (n=158), compared to 24 days (18 to 36) in the control group. The difference is 1 day, this is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because the studies were either not blinded or because of high numbers lost to follow-up (risk of bias, -1) and variance of point estimates across studies (inconsistency, -1). The level of evidence for the outcome 'duration of hospitalization' is considered *low*.

Time to clinical improvement (important)

Time to clinical improvement was reported in four studies for hospitalized patients with COVID-19 (Ader, 2021; Beigel, 2020; Spinner, 2021; Wang, 2020). Due to differences in reporting, data were not pooled.

Ader (2021) reported that the median (IQR) days to NEWS-2 of 2 or lower or hospital discharge within 29 days was 9 days (5 to 14) in the intervention group (n=253), compared to 8 days (5 to 13) in the control group (n=251). The difference is 1 day, in favour of the control group. In addition, they reported that the median (IQR) time to improvement of two categories of the 7-point ordinal scale or hospital discharge within day 29 was 11 days (8 to 20) in the intervention group, compared to 9 days (6 to 15) in the control group. The difference is 2 days, in favour of the control group. This is not considered clinically relevant.

Beigel (2020) reported that the median time (95% CI) to discharge or NEWS ≤ 2 for 24 hours was 8 days (7 to 9) in the intervention group (n=541), compared to 12 days (10 to 15) in the control group (n=521). The difference was 4 days, in favour of the intervention group. This is considered clinically relevant.

Spinner (2021) reported the number of patients who showed clinical improvement at day 28. Clinical improvement was defined as an improvement of at least 2 points from baseline on the 7-point ordinal scale. Spinner (2021) reported that 345 (89.8%) of the patients in the intervention group (n=384) showed clinical improvement, compared to 166 (83.0%) of the control group (n=200). This results in a RR of 1.08 (95%CI 1.01 to 1.16). The RD is 0.07 (95%CI 0.01 to 0.13) in favour of the intervention group. This is considered clinically relevant.

Wang (2020) reported the median time to clinical improvement defined as a two-point reduction in patient's admission status on a six-point ordinal scale, or live discharge from the hospital, whichever came first. The intervention group (n=158) had a median (IQR) time to improvement of 21 days (13 to 28 days), compared to 23 days (15 to 28) in the control group (n=78). The difference is 2 days, in favour of the intervention group. This is not considered clinically relevant.

Ader (2021) reported that the median (IQR) days to NEWS-2 of 2 or lower or hospital discharge within 29 days was 20 days (12 to 29) in the intervention group (n=161), compared to 26 days (12 to 29) in the control group (n=167). The difference is 6 days, in favour of the intervention group. The difference is considered clinically relevant. In addition, they reported that the median (IQR) time to improvement of two categories of the 7-

point ordinal scale or hospital discharge within day 29 was 16 days (10 to 29) in the intervention group, compared to 17 days (10 to 29) in the control group. The difference is 1 day, in favour of the intervention group. This is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of the studies were not blinded (risk of bias, -1), heterogeneity in reporting 'clinical improvement' and variance of point estimates across studies (inconsistency, -1). The level of evidence for the outcome 'time to clinical improvement' is considered *low*.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with remdesivir compared to treatment without remdesivir in patients with COVID-19?

P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
I: remdesivir + standard care
C: standard care only / placebo treatment + standard care
O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

Relevant outcome measures

For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days difference for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and ICU admission (resulting in a NNT of 20).

Studies of hospitalized patients were categorized on based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation,

extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 14 October 2021. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in indexed journal, comparing treatment with remdesivir and standard care to standard care alone or treatment remdesivir and standard care to placebo and standard care in patients with COVID-19.

The systematic literature search resulted in 77.987 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials. Eventually, seven studies were included.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, seven RCTs were included in the analysis. Important study characteristics and results are summarized below. Studies are presented in alphabetical order, only results of the primary outcome is reported in the summary of literature. Additionally, studies are summarized in the evidence tables. The assessment of the risk of bias is summarized separately in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Corticosteroïden

Uitgangsvraag

Wat is de plaats van corticosteroïden bij de behandeling van COVID-19 patiënten?

Aanbeveling

Behandel patiënten met COVID-19 bij wie zuurstoftoediening geïndiceerd is en met name bij patiënten waarbij de zuurstoftherapie geëscaleerd moet worden naar invasieve respiratoire ondersteuning met **dexamethason 6 mg per dag gedurende maximaal 10 dagen**

Bij patiënten zonder extra zuurstofbehoefte wordt behandeling met corticosteroïden niet aangeraden.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder corticosteroïden. Corticosteroïden die moesten worden geïnhaleerd werden in dit literatuuronderzoek niet opgenomen. Tot en met 2 september 2021 werden er 11 gerandomiseerde gecontroleerde studies (RCTs) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=2989 in de interventiegroep en n=5018 in de controlegroep). De grootste studie die werd meegenomen was de RECOVERY trial (Horby, 2021), met meer dan 6000 geïncloseerde patiënten. Er werden geen studies gevonden die aan de selectiecriteria voldeden met ambulante patiënten.

De geïncloseerde studies onderzochten de volgende corticosteroïden: *dexamethason* (Tomazini, 2020; Jamaati, 2021; Horby, 2021), *hydrocortison* (Angus, 2020; Dequin, 2020; Munch, 2021), of *methylprednisolon* (Jeronimo, 2020; Edalatifard, 2020; Corral-Gudino, 2021; Solanich, 2021; Tang, 2021). De cruciale uitkomstmaten voor de besluitvorming waren mortaliteit en de noodzaak voor invasieve respiratoire ondersteuning. Daar waar mogelijk werd data van verschillende typen corticosteroïden gecombineerd om tot overkoepelende literatuurconclusies te komen over de effecten van corticosteroïden. Wanneer er enkel data aanwezig was over één type corticosteroïd werd het middel in de literatuurconclusies specifiek benoemd. Ook werden de effecten van corticosteroïden op de mortaliteit, in een subgroep analyse, opgesplitst naar ernst van ziekte: patiënten met milde, matige en ernstige COVID-19 symptomen op basis van respiratoire ondersteuning op moment van inclusie.

Er werden alleen randomiseerde trials geïncloseerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat dat er een aantal open-label trials waren (waaronder de RECOVERY trial), met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten, werd de kwaliteit van dit bewijs naar beneden bijgesteld. Daarnaast waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van het betrouwbaarheidsinterval rondom de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld.

Systemische corticosteroïden bij patiënten die waren opgenomen in het ziekenhuis

Met een redelijke zekerheid kan worden geconcludeerd dat er een reductie in de mortaliteit optreedt bij het

gebruik van corticosteroïden (risicoverschil: -4,33%, 95% CI: -8,58% tot -0,07%; relatief risico: 0,89, 95% CI: 0,79 tot 1,02). Dit verschil werd door de werkgroep gedefinieerd als klinisch relevant. De data betroffen grotendeels patiënten met redelijke tot ernstige COVID-19; alleen de RECOVERY trial (Horby, 2021) includeerde ook patiënten met milde COVID-19.

De RECOVERY trial van Horby (2021) splitste de data van de mortaliteit ook op naar ernst van ziekte. De subgroep met ernstige ziekte kon worden gepoold in een meta-analyse samen met data van andere studies die enkel patiënten met ernstige ziekte includeerden (Tomazini, 2020; Angus, 2020). Bij het gebruik van corticosteroïden in de groep patiënten die als ernstig ziek kon worden aangemerkt, werd met een hoge zekerheid geconcludeerd dat er een klinisch relevante reductie in de mortaliteit optreedt (risicoverschil: -9,18%, 95% CI: -14,13% tot -4,23%; relatief risico: 0,82, 95%CI: 0,68 tot 0,98). Dit effect was minder groot, maar nog steeds statistisch significant, bij de patiënten met een matig-ernstige COVID (risicoverschil: -2,9%). Omdat dit verschil minder was dan de vooraf gedefinieerde grens van klinische relevantie (3% punten verschil), wordt in de conclusie beschreven dat dexamethason nauwelijks verschil maakt in de mortaliteit na 28 dagen. Echter, vanwege de grootte en de kwaliteit van de studie van Horby (2021), en de relatief beperkte bijwerkingen van dexamethason, wordt de risicoreductie van 2,9% nog steeds als relevant en betrouwbaar beschouwd. In de groep patiënten met milde COVID-19 (waarbij geen zuurstof suppletie nodig was) was er mogelijk een kleine, maar klinisch relevante, toename in de mortaliteit bij het gebruik van corticosteroïden (in dit geval dexamethason).

Het is nog niet duidelijk waarom er geen mortaliteitswinst is in de 'milde groep' zonder zuurstofbehoefte of bij personen die minder dan 7 dagen ziek waren. Het is daarbij niet helder wat daarbij het meest bepalend was: de ernst van infectie (dus de daling van de zuurstofsaturatie bij een aantal patiënten in die totale groep met een duur van symptomen van 7 dagen of minder) of alleen de duur van de symptomen. Deze bevindingen geven richting aan gebruik van dexamethason: vooral in de latere fase bij matig of ernstig zieke patiënten met extra zuurstofbehoefte waar (hyper)inflammatie op de voorgrond staat. Die zuurstofbehoefte is leidend vanwege de subgroep analyse in de studie van Horby (2021), maar mogelijk is gebruik van dexamethason ook bij slechts een korte duur (< 7 dagen) van symptomen niet effectief. Preventief gebruik in een vroege fase van infectie moet worden afgeraden, behalve als dat vanwege een andere indicatie (bijv. exacerbatie COPD) moet worden voorgeschreven. Een retrospectieve studie pleit voor gebruik van corticosteroïden alleen bij ernstige infecties, hier gedefinieerd door CRP >200 mg/L (vs. CRP <100 mg/L) (Keller, 2020). De RCTs in deze richtlijn gebruiken deze criteria niet en in het advies wordt een dergelijk afkappunt dan ook niet geadviseerd.

Uitkomsten betreffende invasieve respiratoire ondersteuning werden heterogeen gerapporteerd in de studies. Zo werd bijvoorbeeld de noodzaak voor invasieve ventilatie gerapporteerd, maar ook het aantal dagen aan mechanische ventilatie, het aantal dagen zonder respiratoire ondersteuning, de noodzaak voor high flow zuurstof of ventilatoire ondersteuning en de noodzaak voor respiratoire ondersteuning. Hierdoor zijn voor deze specifieke uitkomsten veelal weinig data beschikbaar. Met een lage tot zeer lage zekerheid werd geconcludeerd dat er bij verschillende typen corticosteroïden een klein tot geen effect zou kunnen optreden voor de verschillende uitkomsten die voor invasieve respiratoire ondersteuning werden gerapporteerd of dat het bewijs onzeker was over het effect. De studie van Horby (2021) liet wel een puntschatter zien in het voordeel van corticosteroïden.

Belangrijke uitkomstmaten waren de duur van hospitalisatie en de tijd tot klinische verbetering. Met een lage zekerheid werd geconcludeerd dat er een klein tot geen effect zou kunnen optreden op de duur van hospitalisatie. Het bewijs over het effect van corticosteroiden (in dit geval alleen methylprednisolon) op de tijd tot symptoomresolutie was erg onzeker, waarbij data over andere middelen ontbrak.

Soort corticosteroiden bij patiënten die waren opgenomen in het ziekenhuis

Omdat de geïncludeerde studies verschillende middelen onderzochten werden ze ook geclusterd geanalyseerd op basis van het middel dat verstrekt werd in de studie: *dexamethason* (Tomazini, 2020; Jamaati, 2021; Horby, 2021), *hydrocortison* (Angus, 2020; Dequin, 2020; Munch, 2021), of *methylprednisolon* (Jeronimo, 2020; Edalatifard, 2020; Corral-Gudino, 2021; Solanich, 2021; Tang, 2021). Zie de bijlage voor de literatuurbeoordelingen en -conclusies per middel. Een head-to-head vergelijking van de verschillende corticosteroiden is op dit moment niet beschikbaar.

Voor alle verschillende corticosteroiden was de gepoolde puntschatter van de risk ratio in het voordeel van het betreffende middel. Op basis van deze risk ratio's is er geen voordeel uit te spreken voor een bepaald type corticosteroiden. Wel is er veruit het meeste bewijs beschikbaar voor dexamethason, omdat de grootste geïncludeerde studie (Horby, 2021) hier onderzoek naar deed. In het advies wordt er om deze reden een voorkeur voor dexamethason uitgesproken.

Duur van de behandeling met corticosteroiden

In de geïncludeerde studies worden niet alleen verschillende middelen onderzocht, ook de duur en de dosis van de behandeling is verschillend. De behandelduur varieert van enkele dagen tot 28 dagen. Het meeste bewijs komt uit de studie van Horby (2021), waar patiënten gedurende 10 dagen met 6 mg dexamethason werden behandeld of tot en met de dag dat ze uit het ziekenhuis werden ontslagen. In het advies zullen wij deze behandelduur aanhouden.

Overige overwegingen

Dosering

Klinische dose-finding studies voor corticosteroiden zijn niet gedaan. Er is op dit moment onvoldoende data over het gebruik van hogere doses corticosteroiden dan de dosis gebruikt in de RECOVERY-studie. Een recente RCT uit Iran met 86 patiënten laat zien dat 2 mg/kg/dag methylprednisolon geassocieerd is met een sneller klinisch herstel, kortere opname duur en kleinere kans op progressie naar invasieve beademing, vergeleken met 6 mg dexamethason per dag (Ranibar, 2021). Echter, deze studie is relatief klein en van matige kwaliteit en vergelijkt bovendien twee verschillende doseringen van twee verschillende middelen. Een grote RCT in Europa en India met 982 deelnemers met tenminste 10 liter zuurstofbehoefte (COVID STEROID 2 Trial group, 2021), randomiseerde naar 12 mg of 6 mg dexamethason. Er werd geen statistisch significant verschil gezien qua dagen vrij van orgaanondersteuning (22,0 dagen bij 12 mg versus 20,5 dagen bij 6 mg dexamethason) of mortaliteit na 28 dagen (27,1% bij 12 mg versus 32,3% bij 6 mg dexamethason). Wel rapporteren de auteurs dat de uitkomsten allebei neigen naar een voordeel van een hogere dosering dexamethason zonder dat er een verschil was in de hoeveelheid bijwerkingen. Een Italiaanse RCT

randomiseerde 301 patiënten naar methylprednisolon boven op de standaard behandeling met dexamethason 6 mg (Salvarani, 2022). In deze studie werd geen voordeel gezien van aanvullende behandeling met methylprednisolon.

Al met al is er op dit moment geen positief bewijs voor behandeling met een hogere dosering corticosteroïden dan 6 mg dexamethason. Daarnaast is het nog onduidelijk of een hogere dosering corticosteroïden de toevoeging van een IL-6 remmer (zoals tocilizumab) onnodig maakt bij ernstig zieke patiënten, zoals dat op dit moment gebruikelijk is. Ook is het onduidelijk of een hogere dosering corticosteroïden in combinatie met een IL-6 remmer tot meer complicaties zou leiden in deze populatie. In de COVID STEROID 2 studie werd IL-6 therapie toegepast in een minderheid van de patiënten (11% van de 12 mg dexamethason groep en 10% van de 6 mg dexamethason groep). Eerdere onderzoeken bij andere virale luchtweginfecties lieten zien dat de mortaliteit toenam bij het gebruik van hogere doseringen corticosteroïden. Vandaar dat er op dit moment wordt afgeraden om hogere doseringen corticosteroïden toe te passen buiten studieverband.

Bijwerkingen

Omdat er zeer heterogene definities werden gebruikt bij het rapporteren van bijwerkingen en er een hoog risico op bias was, werden deze gegevens niet systematisch weergegeven in de module. Een Cochrane review zet de bijwerkingen van diverse studies op een rij (Wagner, 2021). Er wordt geen meta-analyse verricht, maar een analyse van de descriptieve statistiek van de studies resulteert wel in de conclusie dat er geen grote verschillen in (ernstige) bijwerkingen werden gezien in de groep met en zonder corticosteroïden. Ook als er specifiek naar in het ziekenhuis opgelopen infecties werd gekeken, werden er geen grote verschillen gezien.

Ondanks dat de verschillen in bijwerkingen en ongewenste effecten van corticosteroïden niet in deze studies naar voren komen, is het wel bekend dat corticosteroïden geassocieerd zijn met onder andere een ontregeling van diabetes mellitus, het optreden van neuropsychiatrische symptomen en predisponeren voor infecties. Bij hoge doseringen corticosteroïden werd er ook een associatie met ernstige schimmelinfecties beschreven zoals aspergillose en mucormycose (Hoenigl, 2022).

Speciale patiëntengroepen

Het is logisch om het advies over corticosteroïden voor volwassenen naar zeer ernstig zieke kinderen te extrapoleren. Helaas kan dit niet goed worden onderbouwd met gerandomiseerd onderzoek. Bij kinderen is er nu nog weinig bewijs dat COVID-19 met meer complicaties gepaard gaat, de ziekte lijkt bij kinderen juist met minder complicaties gepaard te gaan. Dat zou pleiten voor terughoudendheid voor het voorschrijven van corticosteroïden bij minder zieke pediatrische patiënten (niet op IC opgenomen).

In de bovengenoemde trials werden ook oudere patiënten geïncludeerd. In een subgroep analyse van de RECOVERY trial, bij ruim 900 patiënten die ouder waren dan 70 jaar, werd een mogelijk minder sterk voordeel van dexamethason zien op de 28-dagen mortaliteit (Horby, 2021). Bij de kwetsbare oudere patiënt kan dexamethason een hoger risico geven op een delier, waardoor een afweging van de baten en te verwachte bijwerkingen extra belangrijk is.

Inhalatiecorticosteroïden

Therapie met inhalatiecorticosteroïden (ICS) is tot nu toe vooral overwogen bij ambulante patiënten. Het gebruik van ICS is relatief eenvoudig en kent, zeker als de behandeling kortdurend is, weinig bijwerkingen. Er zijn tot nu toe vier gerandomiseerde studies gepubliceerd die rapporteren over het effect van ICS bij patiënten met COVID-19.

In een open-label fase 2-gerandomiseerd onderzoek (de STOIC-trial) werd het effect van de inhalatie van budesonide (2dd 800 ug) onderzocht bij patiënten die waren gediagnosticeerd met covid-19 en nog geen opname-indicatie hadden (Ramakrishnan, 2021). Deze studie werd voortijdig gestopt na inclusie en 1:1-randomisatie van 146 patiënten. Het primaire eindpunt was de behoefte aan 'urgente medische zorg'. Dit kwam frequenter voor in de groep met standaardzorg dan in de groep die budesonide gebruikte (11 versus 2 maal, dit was statistisch significant). Patiënten die ICS gebruikte waren gemiddeld 1 dag eerder klachtenvrij. De hoeveelheid virus die op verschillende momenten was gemeten middels nasofarynxuitstrijk verschilde niet tussen beide groepen. Een andere open-label fase 2-gerandomiseerde studie onderzocht het effect van ciclesonide inhalatie (2dd 320 ug) gedurende 14 dagen (Song, 2021). Patiënten waren ambulant en hadden een recente diagnose COVID-19 (binnen 7 dagen na start symptomen of binnen 3 dagen na diagnose). Er werden 61 patiënten geïnccludeerd. In de groep met ICS werd een snellere daling van de viral load gezien en een kleinere kans op klinisch falen. Echter, het aantal patiënten in de studie was klein en deze positieve effecten werden niet in alle secundaire uitkomstmaten terug gezien.

In de grootste trial, de open-label PRINCIPLE trial (Yu, 2021), werden ambulante patiënten geïnccludeerd met verhoogd risico op een ernstig beloop. Inclusiecriteria waren o.a. een leeftijd ≥ 50 jaar met minimaal 1 comorbiditeit, of een leeftijd ≥ 65 jaar, met of zonder comorbiditeit. Eindpunten waren de door de patiënt zelf gerapporteerde tijd tot herstel, en noodzaak tot ziekenhuisopname in de eerste 28 dagen. Na randomisatie en exclusie vanwege het ontbreken van een positieve test voor SARS-CoV-2, werden er 787 personen in de budesonide behandelgroep en 1069 in de controlegroep geanalyseerd. Patiënten die budesonide turbuhaler gebruikten rapporteerden gemiddeld 3 dagen eerder hersteld te zijn. In de standaardzorg groep werden iets meer patiënten binnen 28 dagen na randomisatie in het ziekenhuis opgenomen (8,8% vs. 6,8%; OR 0,75 in het voordeel van budesonide; CI 95% 0,55-1,03). Superioriteit van budesonide voor deze uitkomstmaat werd statistisch niet aangetoond.

De RCT van Clemency (2022) randomiseerde 400 ambulante patiënten naar 2 maal per dag ciclesonide 320 ug of placebo gedurende 30 dagen. Inclusie in de studie was onafhankelijk van de duur van de klachten of onderliggend lijden. Gemiddeld waren de patiënten 43 jaar, 55% was vrouw. Het primaire eindpunt van de studie was de tijd tot alle symptomen van COVID-19 verdwenen waren. In beide groepen was dit 19 dagen. Er werd ook geen verschil gezien in het percentage mensen dat op dag 30 nog symptomen had: 70,6% was klachtenvrij in de ciclesonide groep versus 63,5% in de placebo groep (OR 1,28; 95% CI 0,84-1,97). Wel werden er minder bezoeken aan de spoedeisende hulp of opnames gezien in de groep met ciclesonide: 1% versus 5,4% (OR 0,18; 95% CI 0,04-0,85). Niemand overleed tijdens de studie.

De vier gerapporteerde RCT's beschrijven allen in meer of mindere mate een positief effect van ICS. Twee studies waren relatief klein; de PRINCIPLE studie had methodologische beperkingen, onder meer omdat de behandeling niet geblindeerd was en de tijd tot herstel door patiënten 'self-reported' was. De RCT van Clemency (2022) heeft door de blinding beduidend minder beperkingen. In zowel de studie van Clemency

(2022) als de PRINCIPLE trial (Yu, 2021) was het aantal patiënten dat zou zijn behandeld zijn om 1 ziekenhuisopname te voorkomen echter hoog, 50 (number needed to treat). De STOIC trial bevatte te weinig inclusies om de werkzaamheid betrouwbaar vast te stellen. Data over het voorkomen van harde eindpunten als IC opname, noodzaak tot mechanische ventilatie en overlijden, ontbreken. Er zijn geen gegevens uit deze of andere studies die wijzen op een schadelijk effect van ICS, ook een Cochrane review die 3 RCT's includeerde, vond geen verhoogd aantal 'adverse events' bij het gebruik van ICS (Griesel, 2022).

Op basis van bovengenoemde data heeft de NHG een behandeladvies opgesteld voor ambulante patiënten (zie NHG standaard COVID-19, corona.nhg.org. Bij opgenomen patiënten is er geen plaats voor behandeling met inhalatiecorticosteroiden.

In maart 2022 adviseerde de Amerikaanse NIH (National Institutes of Health) niet voor of tegen het gebruik van ICS, de Amerikaanse IDSA (Infectious Diseases Society of America) adviseerde tegen het gebruik van ICS. De IDSA nam in haar advies ook de studie van Ezer (2021) mee, die geen positief effect van ciclesonide liet zien. Deze studie was echter vroegtijdig gestopt en was mogelijk 'underpowered'.

Virusvarianten

Sinds de opkomst van de omikron variant van SARS-CoV-2 in Nederland eind 2021, is de kans op een ernstig beloop van COVID-19 op populatieniveau zeer sterk gedaald. Het is van belang om op te merken dat de besproken gerandomiseerde studies werden verricht voor de opkomst van de omikron variant. Het is onduidelijk wat de invloed is van deze variant op het effect van anti-inflammatoire therapie, al wordt aangenomen dat patiënten die door de omikron variant een ernstige COVID-19 infectie ontwikkelen nog steeds baat hebben bij anti-inflammatoire therapie. De 'number needed to treat' zou wel anders (vermoedelijk hoger) kunnen zijn.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Er werd een klinisch relevant voordeel gevonden bij opgenomen patiënten met een ernstige COVID-19 infectie die behandeld werden met dexamethason, vergeleken met de groep die dit niet kreeg. In patiënten met een matig ernstige COVID-19 infectie werd er ook voordeel vastgesteld, al was dit minder groot dan bij patiënten met een ernstige ziekte.

Het is voor patiënten belangrijk om te weten wat de voor en nadelen van dexamethason zijn, zoals bijvoorbeeld de ontregeling van de glucose waarden bij patiënten met pre-existente diabetes mellitus (zie ook het kopje 'bijwerkingen'). Deze nadelen zullen in de groep patiënten met een matig ernstige COVID-19 infectie zwaarder wegen dan bij patiënten met een ernstige COVID-19, waar deze mogelijke bijwerkingen veelal opwegen tegen de sterke voordelen.

Kosten (middelenbeslag)

Een behandeling met dexamethason gedurende 10 dagen kost ongeveer 50 euro indien dit intraveneus gegeven wordt en 10 euro indien dit oraal gegeven wordt. Dit is relatief weinig vergeleken met de kosten die gemaakt worden bij de opname van patiënten met COVID-19.

Aanvaardbaarheid, haalbaarheid en implementatie

Dexamethason lijkt effectief om een ernstig beloop van de ziekte te voorkomen en de kosten zijn beperkt. De bijwerkingen, zoals bij de overwegingen beschreven, kunnen echter de aanvaardbaarheid beperken.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Bij patiënten met COVID-19 bij wie zuurstoftoediening geïndiceerd is vanwege saturatiedaling, en met name bij patiënten waarbij de zuurstoftherapie geëscaleerd moet worden naar invasieve respiratoire ondersteuning, is behandeling met **dexamethason 6 mg per dag** (of een equivalente dosis hydrocortison/prednison) **gedurende 10 dagen of tot ontslag uit het ziekenhuis**, aangewezen. Bij patiënten zonder extra zuurstofbehoefte wordt behandeling met corticosteroïden niet aangeraden. Voor de behandeling van kinderen kunnen de doseringen beschreven in het Kinderformularium worden gebruikt.

Onderbouwing

Achtergrond

Een dysregulatie van de immuunrespons lijkt bij COVID-19 een belangrijke rol in de pathofysiologie te spelen (Veerdonk, 2021). Er worden verschillende middelen ingezet en onderzocht met anti-inflammatoire werking. Corticosteroïden zijn goed beschikbaar en werden bij infecties met SARS-CoV-1 en MERS-CoV virussen frequent voorgeschreven in de hoop dat daarmee immuun-gemedieerde schade voorkomen kon worden. Omdat corticosteroïden ook kunnen zorgen voor een toename of langere duur van virale replicatie was er veel twijfel over gebruik ervan als behandeling (Lee, 2004; Arabi, 2018). In algemene zin wijzen de verschillende meta-analyses naar de toepassing van corticosteroïden bij ARDS in de richting van verbeterde uitkomsten met corticosteroïden (Meduri, 2016; Peter, 2008; Yang, 2017). Bij influenza geassocieerde ARDS is er echter een aanwijzing voor verhoogde mortaliteit (Tsai, 2020).

Een eerste retrospectieve analyse van opgenomen SARS-CoV-2 patiënten in Wuhan, China, toonde dat de sterfte van patiënten die een ARDS ontwikkelden lager was in de groep die behandeld werd met methylprednisolon dan in de groep zonder (Wu, 2020). De gebruikte dosis werd niet vermeld. Klinische dose-finding studies zijn niet gedaan. Inmiddels is in diverse gerandomiseerde studies (RCTs) de effectiviteit van corticosteroïden onderzocht om de plaats van corticosteroïden bij de behandeling van COVID-19 patiënten te bepalen.

Conclusies / Summary of Findings

Systemic corticosteroids in hospitalized COVID-19 patients

Mortality (crucial)

Moderate GRADE	Treatment with corticosteroids (all combined) probably reduces mortality (overall) when compared with treatment without corticosteroids in <u>hospitalized</u> COVID-19 patients. <i>Source: Angus, 2020; Corral-Gudino, 2021; Dequin, 2020; Edalatifard, 2020; Horby, 2021; Jamaati, 2021; Jeronimo, 2020; Much, 2021; Solanich, 2021; Tang, 2021; Tomazini, 2020</i>
High GRADE	Treatment with corticosteroids (all combined) reduces mortality when compared with treatment without corticosteroids in <u>hospitalized</u> patients with <u>severe</u> COVID-19. <i>Source: Angus, 2020; Horby, 2021; Tomazini, 2020</i>
Moderate GRADE	Treatment with dexamethasone probably results in limited difference of mortality when compared with treatment without dexamethasone in <u>hospitalized</u> patients with <u>moderate</u> COVID-19. <i>Source: Horby, 2021</i>
Low GRADE	Treatment with dexamethasone may increase mortality when compared with treatment without dexamethasone in <u>hospitalized</u> patients with <u>mild</u> COVID-19. <i>Source: Horby, 2021</i>

Extensive respiratory support (crucial)

Low GRADE	Treatment with corticosteroids may result in little to no difference in the need for extensive respiratory support when compared with treatment without corticosteroids in <u>hospitalized</u> COVID-19 patients. <i>Source: Angus, 2020; Corral-Gudino, 2021; Dequin, 2020; Edalatifard, 2021; Horby, 2021; Jamaati, 2021; Jeronimo, 2020; Solanich, 2021; Tang, 2021; Tomazini, 2020</i>

Duration of hospitalization

Low GRADE	Treatment with corticosteroids may result in little to no difference in the length of stay when compared with treatment without corticosteroids in <u>hospitalized</u> COVID-19 patients. <i>Source: Horby, 2021; Angus, 2020; Jamaati, 2021; Jeronimo, 2020; Tang, 2021</i>

Time to clinical improvement

Very low GRADE	The evidence is very uncertain about the effects of methylprednisolone on the time to clinical improvement when compared with treatment without methylprednisolone in <u>hospitalized</u> COVID-19 patients. <i>Source: Solanich, 2021; Tang, 2021</i>

Corticosteroids in non-hospitalized COVID-19 patients

No GRADE	No studies were found investigating the effect of corticosteroids on mortality, respiratory support, duration of hospitalization, or time to clinical improvement compared to standard care in non-hospitalized COVID-19 patients. <i>Sources: -</i>

Samenvatting literatuur

Systemic corticosteroids in hospitalized COVID-19 patients

DEXAMETHASONE

Tomazini (2020) (CoDEX trial) described a multicenter, open-label randomized clinical trial in Brazil comparing intravenous dexamethasone and standard care with standard care only in patients admitted to an ICU with suspected or confirmed COVID-19. The trial was terminated early. Patients were included when intubated and mechanically ventilated within 48 hours of meeting the criteria for moderate or severe ARDS. Patients were excluded when they e.g. used corticosteroids in the past 15 days (when non-hospitalized) or were immunosuppressed. A total of 299 patients were randomized to receive standard care and dexamethasone or to receive standard care only. The dexamethasone-group received 20 mg dexamethasone once daily intravenously for the first five days, followed by 10 mg intravenously for the following 5 days or until ICU discharge. In the standard care only-group 35.1% of the patients had deviations from the assigned control intervention and received corticosteroids as well. Follow-up in both the intervention and control group was 28 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, and serious adverse events. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Tomazini (2020) contained patients with severe disease at baseline. The primary outcome was mechanical ventilatory-free days during the first 28 days. The corticosteroid group had a mean ventilatory-free days of 6.6 (95% CI: 5.0 to 8.2), compared to 4.0 days (95% CI: 2.9 to 5.4) in the group not receiving corticosteroids (difference: 2.26 days, 95% CI: 0.2 to 4.38).

Jamaati (2021) reported the preliminary results of a randomized controlled trial in a hospital in Iran comparing intravenous dexamethasone and standard care to standard care only. The trial was terminated after no significant clinical response was observed in 50 patients. Patients were included when e.g. they had a $\text{PaO}_2/\text{FiO}_2$ ratio between 100-300mmHg. Exclusion criteria were e.g. chronic kidney or liver disease, or hyperglycemia. The 50 included patients were randomized to dexamethasone with standard care (n=25) or to standard care only (n=25). Standard care consisted of oxygen support, fluid support, and lopinavir/ritonavir (200/50 mg, two tablets twice daily) according to Iranian guidelines. Dexamethasone at a dose of 20mg per day was administered intravenously up to day 5, whereafter 10mg per day was administered intravenously up to day 10. At baseline, the standard care only-group had more patients with pulmonary disease (36%) compared to the dexamethasone-group (4%). Follow-up in both groups was 28 days. The following outcomes relevant to this guideline module were reported: mortality, need for non-invasive ventilation, and duration of hospitalization. The disease status in Jamaati (2020) was mild to moderate disease, patients were included when the $\text{PaO}_2/\text{FiO}_2$ ratio was between 100 and 300 mmHg. The primary outcomes were both the need for extensive mechanical ventilation and the death rate. In the corticosteroids group 52.0% required invasive mechanical ventilation compared to 44.0% in the control group (RR=1.18, 95% CI: 0.66 to 2.11; RD=8%. 95%

CI: -19.6% to 35.6%). Sixteen deaths (16/25, 64.0%) were observed in the corticosteroids group, compared to 15 deaths (15/25, 60.0%) in the group not receiving corticosteroids (RR=1.07, 95% CI: 0.69 to 1.65; RD=4%, 95% CI: -22.9% to 30.9%).

Horby (202) (RECOVERY trial) described an open-label randomized clinical trial in the United Kingdom assessing the effect of dexamethasone and standard care compared to standard care only. Patients were included when hospitalized, and had no medical history that would put the patient substantially at risk when participating in the study. Exclusion criteria were not specified. A total of 6.425 patients were included and randomized to dexamethasone and standard care or to standard care only. Standard care was provided as the usual standard of care in the participating hospital but was not further defined in the trial report. Patients in the dexamethasone-group received 6mg oral or intravenous dexamethasone daily for up to 10 days or until discharge, whichever came first. Here, 95% of the patients received at least one dose of a glucocorticoid. The standard care group received the usual care, however 8% of these patients also received a glucocorticoid. Follow-up in both groups was 28 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, and serious adverse events. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Horby (2020) contained patients with mild to severe disease at baseline. The primary outcome was the 28-day all-cause mortality. Here, 482 deaths (482/2104, 22.9%) were observed in the dexamethasone group, compared to 1.110 deaths (1110/4321, 25.7%) in the usual care group (RR=0.89, 95% CI: 0.81 to 0.98; RD=-2.8%, 95% CI: -5% to -0.6%).

HYDROCORTISONE

Angus (2020) (REMAP-CAP) examined the effects of hydrocortisone compared to usual care as part of a multicenter open-label adaptive platform randomized controlled trial. Centers were located in Australia, Canada, France, Ireland, the Netherlands, New Zealand, the United Kingdom, and the United States of America. The domain examining corticosteroids was terminated early due to a loss of equipoise, while no study data were reviewed prior to the decision to stop enrollment of patients. Patients were included when admitted to the intensive care unit for respiratory or cardiovascular organ support. Patients were excluded when e.g. death was deemed imminent and inevitable, or soon discharge was expected, or when more than 36 hours elapsed since admission to the intensive care unit, or when the treating clinician believed that participating would not be in the best interest of the patient. Patients were randomly allocated to one of the three study-arms: fixed dose hydrocortisone, shock-dependent hydrocortisone, and a standard of care without hydrocortisone. Standard care was provided as per each center's standard. Systemic corticosteroids were permitted in all groups when new indications developed for which corticosteroids would be an established treatment. In the group who were randomized to standard care without hydrocortisone, 15% (n=15) received a systemic corticosteroid (of which n=6 received hydrocortisone). Patients in the fixed dose-group received 50 mg hydrocortisone intravenously every 6 hours for 7 days (n=2 received 100 mg fixed dose). Patients in the shock-dependent-group received 50 mg hydrocortisone intravenously every 6 hours while in shock and up to 28 days. Shock was defined as the requirement for treatment for shock due to COVID-19 by intravenous vasopressor infusion. Hydrocortisone was discontinued when the shock was considered to be resolved or when vasopressors were discontinued for 24 hours. Follow-up of the primary outcome was 21 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, duration of hospitalization and serious adverse events. Following the predefined criteria by the working group for mild,

moderate, and severe disease status at randomization, the sample in Angus (2020) contained patients with severe disease at baseline (with the exception of one patient in the shock-dependent-group who did not receive any acute respiratory support or received supplemental oxygen only). The primary outcome was alive and free of respiratory or cardiovascular organ support- up to 21 days. Median organ support-free days were reported for the fixed-dose group (0 days, IQR: -1 to 15), the shock-dependent group (0 days, IQR: -1 to 13), and the no hydrocortisone group (0 days, IQR: -1 to 11).

Dequin (2020) (CAPECOVID trial) described a multicenter randomized controlled trial examining the effects of hydrocortisone compared to a placebo on intensive care units in France. The trial was terminated early pending the results of the RECOVERY trial and changes in treatment recommendations. Patients were included when admitted to a participating intensive care unit for acute respiratory distress syndrome, and when the experimental treatment was administered within 24 hours of the onset of one of the severity criteria (or within 48 hours when patients were referred from another hospital). Patients were excluded when in septic shock or when there were do-not-intubate orders. Included patients were randomized to hydrocortisone (n=76) or to placebo (n=73). The hydrocortisone dose was 200 mg/day until day 7, 100 mg/day for the next 4 days, and 50 mg/day for the last 3 days of a 14-day treatment regime. When the patient's respiratory status had sufficiently improved by day 4 a short treatment regime of 8 days was initiated instead (200 mg/day until day 4, 100 mg/day for the next 2 days, and 50 mg/day for the last 2 days). Patients in the placebo-group received saline. Adjunctive therapy was allowed in both groups at the discretion of the treating primary physicians. In the hydrocortisone group, n=44 (57.9%) received one or more adjunctive therapies, compared to n=47 (64.4%) in the placebo-group. Adjunctive therapies provided consisted of hydroxychloroquine (whether or not in combination with azithromycin), ritonavir-lopinavir, eculizumab, remdesivir, and/or tocilizumab. The follow-up was 21 days for the post-hoc outcomes. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, and serious adverse events. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Dequin (2020) contained patients with moderate (n=9 had a non-rebreathing mask) to severe disease at baseline. The primary outcome was treatment failure on day 21, a composite of death or the persistent dependency on mechanical ventilation or high-flow oxygen therapy. Treatment failure was observed in 32 patients (32/76, 42.1%) receiving hydrocortisone, compared to 37 patients (37/73, 50.7%) in the placebo group (difference: -8.6%, 95% CI: -24.9% to 7.7%, p=0.29).

Munch (2021) (COVID STEROID trial) described a multicenter randomized controlled trial examining the effects of hydrocortisone compared to a placebo in Denmark. The trial was terminated early due to an unexpected inability to enroll patients. Patients were included when they had severe hypoxia (i.e. use of mechanical or non-mechanical ventilation, or continuous use of CPAP for hypoxia, or oxygen supplementation of at least 10 L/minute independent of delivery system). Patients were excluded when e.g. they used systemic corticosteroids, had invasive mechanical ventilation more than 48 hours before screening. Participating patients were randomized to hydrocortisone (n=16) or placebo (n=14), both with standard care. The hydrocortisone-group received 200 mg per day using continuous infusion over the course of 24 hours or per bolus injection of 50mg each 6 hours. Treatment continued up to 7 days or until hospital discharge. The placebo-group received 0.9% saline continuously infused over the course of 24 hours or as bolus injections every 6 hours. Additional antiviral treatment provided were remdesivir (n=4) or convalescent plasma (n=2). Antibacterial agents were provided in 12 participants (86%). In the hydrocortisone group, n=8 had major

protocol deviations, compared to $n=3$ in the placebo group. The follow-up was 90 days. The following outcomes relevant to this guideline module were reported: mortality and serious adverse events. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Munch (2020) contained patients with moderate to severe disease at baseline. The primary outcome was days alive without the use of life support up to day 28. No difference was observed between groups (adjusted mean difference: -1.1 days, 95% CI: -9.5 to 7.3).

METHYLPREDNISOLONE

Jerónimo (2020) (Metcovid trial) reported a randomized controlled trial examining the effects of sodium succinate methylprednisolone compared to a placebo in Brazil. Patients were included when they had a clinical suspicion of COVID-19 (fever and any respiratory symptom), were 18 years or older, had an $\text{SpO}_2 \leq 94\%$ with room air, and required supplemental oxygen or invasive mechanical ventilation. Patients were excluded when they had e.g. chronic use of corticosteroid or immunosuppressive agents, had decompensated cirrhosis, or had chronic renal failure. Participating patients were randomized to sodium succinate methylprednisolone ($n=209$) or placebo ($n=207$). The methylprednisolone group received 0.5 mg/kg intravenously twice daily over the course of five days. Patients in the placebo group received a saline solution intravenously twice daily for five days. All participating patients meeting criteria for acute respiratory distress syndrome received preemptive ceftriaxone (1g twice daily, 7 days) plus azithromycin (500 mg/day, 5 days) or clarithromycin (500 mg twice daily, 7 days) intravenously. The follow-up was 28 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, duration of hospitalization, and viral clearance. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the cohort contained patients with moderate to severe disease or had an unclear respiratory status (33.8% received invasive mechanical ventilation, 47.8% received non-invasive oxygen therapy, 18.4% unreported). The primary outcome was the 28-day mortality. There were 72 observed deaths (72/194, 37.1%) in the methylprednisolone group compared to 76 (76/199, 38.2%) observed deaths in the placebo group (RR=0.97, 95% CI 0.75 to 1.25; RD=-1.1%, 95% CI -10.7% to 8.5%).

Edalatifard (2020) reported a randomized controlled trial examining the effects of methylprednisolone compared to no methylprednisolone in Iran. Patients were included when 18 years or older, had confirmed COVID-19 (positive RT-PCR and abnormal CT-scan findings) with an $\text{SpO}_2 < 90\%$ at rest, had C-reactive protein > 10 mg/L and interleukin-6 > 6 pg/ml before connecting to the ventilator and intubation, and when agreed to give informed consent. Patients were excluded when they had e.g. an $\text{SpO}_2 < 70\%$, had a positive pro-calcitonin and troponin test, had acute respiratory distress syndrome, uncontrolled diabetes mellitus, gastrointestinal problems or bleeding history, heart failure, or active malignancies, or received any immunosuppressive agents. Participating patients were randomized to receive standard care with methylprednisolone pulse ($n=34$) or standard care without methylprednisolone or other glucocorticoids ($n=34$). The standard care consisted of hydroxychloroquine sulfate, lopinavir, and naproxen. Patients allocated to methylprednisolone pulse received 250 mg per day from an intravenous injection for three days. Six persons in the group receiving standard care without methylprednisolone had received corticosteroids and were excluded. The follow-up was 3 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, and serious adverse events. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Edalatifard (2020) contained patients with moderate to severe disease at baseline. The primary outcomes were the time

to clinical improvement, and a composite of the time to hospital discharge or death (whichever came first). Median time to improvement was 11.84 days in the methylprednisolone group compared to 16.44 days in the standard care group ($p=0.011$). Median time to discharge or death was 11.62 days versus 17.61 days for the methylprednisolone group and the standard care group, respectively.

Corral-Gudino (2021) (GLUCOCOV trial) described a multicenter open-label randomized controlled trial assessing the effect of methylprednisolone with standard care compared to standard care only in Spain. The trial was terminated before the intended sample size was achieved. Patients were included when they e.g. had symptoms for at least 7 days, had moderate to severe disease with abnormal gas exchange ($\text{PaO}_2/\text{FiO}_2$ or $\text{PaFi} < 300$, $\text{SaO}_2/\text{FiO}_2$ or $\text{SaFi} < 400$, or at least two criteria of the BRESCIA-COVID Respiratory Severity Scale), and had evidence of a systemic inflammatory response (any criterium: $\text{CRP} > 150$ mg/L, D-dimer > 800 ng/ml, ferritin > 100 mg/dl, IL-6 > 20 pg/ml). Exclusions were made when patients were mechanically ventilated, hospitalized in the intensive care unit, were treated with corticosteroids or immunosuppressive agents at the time of enrollment, had chronic kidney disease on dialysis, or were pregnant. Sixty-four participants were randomized to receive methylprednisolone with standard care ($n=35$) or to receive standard care only ($n=29$). Standard care was provided according to the local hospital protocols based on the recommendations of the Spanish Ministry of Health and the World Health Organization. The authors stated that the local standard of care protocols among the participating hospitals were similar. The trial also set up a preference arm which allocated the treatment based on preferences rather than randomization. Patients receiving methylprednisolone were administered 40 mg intravenously twice per day for the first three days, whereafter the dose reduced to 20 mg twice per day for the next three days. Additional therapies provided in both groups were azithromycin, hydroxychloroquine, lopinavir/ritonavir, and low molecular weight heparin. The follow-up was 28 days. The following outcomes relevant to this guideline module were reported: mortality and respiratory support. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the sample in Corral-Gudino (2021) contained patients with unclear disease severity at baseline. The respiratory status at inclusion or randomization was not reported, although patients receiving mechanical ventilation or when admitted to the intensive care unit were excluded. The primary outcome was a composite consisting of in-hospital all-cause mortality, escalation to ICU admission, and progression of respiratory insufficiency which would require non-invasive ventilatory support. Although events occurred less frequently in the methylprednisolone group, no statistical differences between groups were found ($\text{RR}=0.68$, 95% CI: 0.37 to 1.26).

Solanich (2021) reported a single-center open-label randomized controlled trial assessing the effects of methylprednisolone and tacrolimus with standard care compared to standard care only in Spain. The trial was terminated early. Patients were included when they had respiratory failure ($\text{PaO}_2/\text{FiO}_2 < 300$, or $\text{SpO}_2/\text{FiO}_2 < 220$), and had high inflammatory parameters ($\text{CRP} > 100$ mg/L, or D-dimer > 1000 $\mu\text{g/L}$, or ferritin > 1000 $\mu\text{g/L}$). Patients were excluded when they had e.g. a glomerular infiltration of 30 ml/min/1.73m² or less, had leukopenia of 4000 cells/ μl or less, had other conditions that cause immunosuppression, had a concomitant potentially serious infection, had contraindications for corticosteroid or tacrolimus use. The intervention-arm ($n=27$) received 120 mg/day methylprednisolone pulses on three consecutive days. Longer duration or a higher dose was allowed when considered appropriate by the treating physician. Besides methylprednisolone, tacrolimus was administered twice daily at 0.05 mg/kg as a starting dose. Tacrolimus dose was thereafter adjusted to achieve 8-10 ng/ml levels in the patient's blood. Standard care could consist

of supplemental oxygen and respiratory support, fluid therapy, anti-pyretic treatment, postural interventions, low molecular weight heparin, antiviral drugs (e.g. lopinavir/ritonavir, hydroxychloroquine), and/or immunosuppressive drugs (e.g. corticosteroids, tocilizumab, anakinra) at the discretion of the treating physician. The standard care-only group (n=28) could not receive cyclosporine or tacrolimus. All patients in the standard care-only group received corticosteroids during hospitalization (median duration of corticosteroid therapy: 18.5 days, IQR: 3.00-53.2 days). The follow-up was 58 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, duration of hospitalization, time to clinical improvement. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the cohort contained patients with moderate to severe disease severity at baseline. The primary outcome was days to reach clinical stability up to 56 days. No statistical differences between groups were found (HR=0.73, 95%CI: 0.39 to 1.37), where the methylprednisolone group had a median of 10.0 days (IQR: 7.0 to 13.0) compared to 11.0 days (IQR: 8.0 to 18.0).

Tang (2021) described a multicenter single-blind randomized controlled trial assessing the effects of methylprednisolone and standard care compared to a placebo and standard care in China. The trial was terminated before the intended sample size was reached. Patients were included when they had a laboratory confirmed SARS-CoV-2 infection, had pneumonia as confirmed by CT, were 18 years or older, were admitted to the general ward for less than 72 hours, and when they were able to sign the informed consent. Patients were excluded when there was e.g. severe immunosuppression, when corticosteroids were needed for other disease, had refractory hypertension or hypokalemia, epilepsy, delirium, glaucoma, active gastrointestinal bleeding (within the last 3 months), or secondary bacterial or fungal infections. Patients allocated to receive methylprednisolone and standard care (n=43) or placebo and standard care (n=43). Standard care was provided according to version 6 of the Chinese Diagnosis and Treatment Plan for COVID-19. The methylprednisolone-group received 1 mg/kg methylprednisolone per day for 7 days. Patients in the placebo-group received 100 ml 0.9% saline intravenously per day for 7 days. The majority (>70%) of patients received additional therapies: such as antiviral and/or antibacterial drugs. The follow-up was 14 days. The following outcomes relevant to this guideline module were reported: mortality, respiratory support, duration of hospitalization, time to clinical improvement. Following the predefined criteria by the working group for mild, moderate, and severe disease status at randomization, the cohort contained patients with moderate to severe or unclear disease severity at baseline as 70.9% received oxygen therapy via nasal cannula and 47.7% had hypoxic respiratory failure. It was not found whether there were patients without any oxygen supplementation. The primary outcome was the occurrence of clinical deterioration within 14 days. Both groups had a clinical deterioration rate of 4.8% (OR=1.00, 95% CI: 0.13 to 7.44).

Table 1. Overview of RCTs comparing corticosteroids with standard care in hospitalized COVID-19 patients.

Author (year, trial name)	Disease severity*	Sample size	Dosage/regime
Dexamethasone			

Tomazini (2020, CoDEX trial)	Severe	N = 299 I: 151 C: 148	I: 20 mg intravenously once daily for 5 days, followed by 10 mg intravenously once daily for additional 5 days or until ICU discharge, whichever occurred first, plus standard care. C: Standard care only
Jamaati (2021)	Mild to moderate	N = 50 I: 25 C: 25	I: Intravenous dexamethasone at a dose of 20 mg/day from day 1–5 and then at 10 mg/day from day 6–10, plus standard care C: Standard care only
Horby (2021, RECOVERY trial)	Mild to severe (sub-group analyses for mild, moderate, and severe disease)	N = 6425 I: 2104 C: 4321	I: 6 mg given once daily for up to 10 days, plus standard care C: Standard care only
Hydrocortisone			
Angus (2020, REMAP-CAP)	Severe	N = 614 I: 137 II: 146 Control: 101	I: fixed-dose hydrocortisone: Patients received a fixed dose of intravenous hydrocortisone, 50 mg or 100 mg, every 6 hours for 7 days. II: shock-dependent hydrocortisone: intravenous hydrocortisone, 50 mg, every 6 hours while in shock for up to 28 days. C: Standard care only
Dequin (2020, CAPECOVID trial)	Moderate to severe	N = 149 I: 76 C: 73	I: Continuous intravenous infusion of hydrocortisone 200mg/day. Treatment was continued at 200mg/d until day 7 and then decreased to 100 mg/d for 4 days and 50 mg/d for 3 days, for a total of 14 days. If the patient's respiratory and general status had sufficiently improved by day 4, a short treatment regimen was used (200mg/d for 4 days, followed by 100mg/d for 2 days and then 50 mg/d for the next 2 days, for a total of 8 days). C: Continuous intravenous infusion of saline, plus standard care

Munch (2021, COVID STEROID trial)	Moderate to severe	N = 30 I: 16 C: 14	I: Intravenous hydrocortisone (200 mg/day) for 7 days or until hospital discharge in addition to standard care; continuous infusion over 24 hrs or as bolus injections every 6 hrs (50 mg per bolus). C: Intravenous saline solution, plus standard care
Methylprednisolone			
Jeronimo (2020, Metcovid trial)	Moderate to severe	N = 397 I: 195 C: 202	I: Intravenous sodium succinate MP (0.5 mg/kg), twice daily for 5 days C: Intravenous saline solution, plus standard care
Edalatifard (2020)	Moderate to severe	N = 68 I: 34 C: 34	I: Intravenous methylprednisolone (MP) Injection (250 mg/day for 3 days), plus standard care C: Standard care and no methylprednisolone or other glucocorticoids
Corral-Gudino (2021, GLUCOCOVID trial)	Unclear	N = 64 I: 35 C: 29	I: Intravenous methylprednisolone (MP) 40 mg, twice a day, for 3 days and then 20 mg, twice a day, for 3 more days. C: Standard care
Solanich (2021)	Moderate to severe	N = 55 I: 27 C: 28	I: Methylprednisolone pulses (120 mg/day) and tacrolimus, plus standard of care C: Standard care
Tang (2021)	Moderate to severe, partially unclear	N = 86 I: 43 C: 43	I: 1 mg/kg per day of methylprednisolone administered intravenously for 7 days, plus standard care C: intravenous saline solution, plus standard care

*Disease severity categories:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

N: Total sample size; I: Intervention; C: Control

Results – Systemic corticosteroids in hospitalized COVID-19 patients

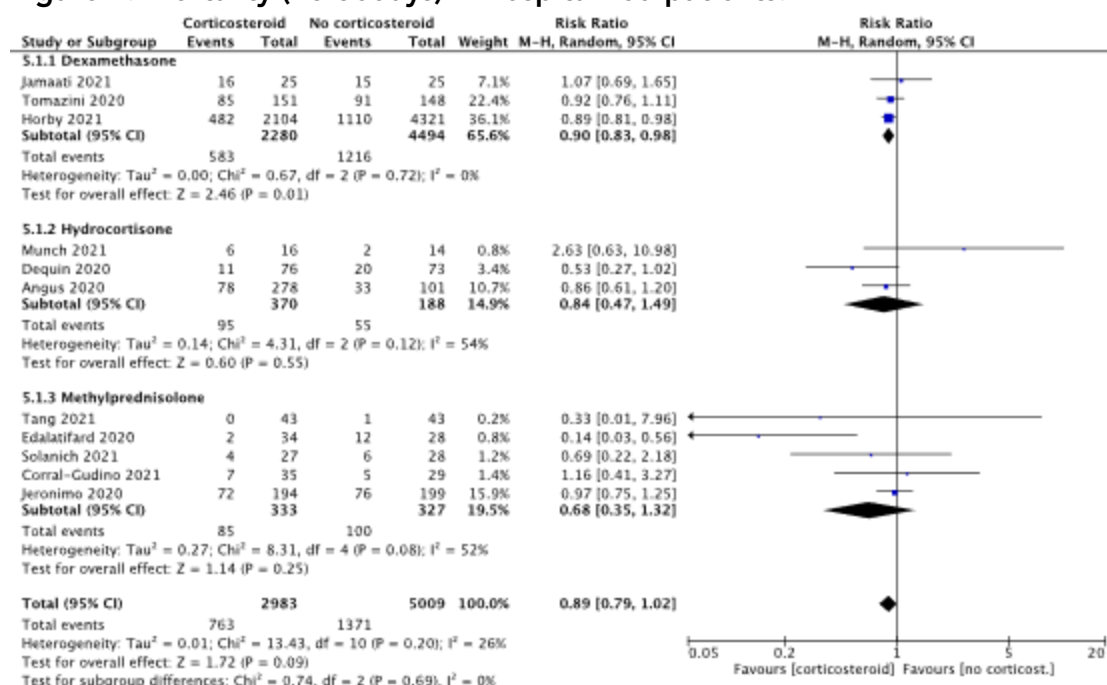
Mortality (crucial)

All of the included RCTs investigated the effect of corticosteroids on mortality. Figure 1 shows the overall

pooled estimate and sub-group analysis by overall disease severity. Overall, there were 763 observed deaths in the corticosteroids group (763/2983, 25.6%) and 1371 observed deaths in the group not receiving corticosteroids (1371/5009, 27.4%). The pooled relative risk was 0.89 (95% CI 0.79 to 1.02), with the summary point estimate favoring the use of corticosteroids. Relative risks for mortality in all individual studies are shown in Figure 1 as well. The pooled risk difference was -4.33% (95% CI -8.58% to -0.07%), with the summary point estimate favoring the use of corticosteroids. When using a risk difference of 3% as a minimally clinically important difference, the pooled point estimate shows a clinically relevant difference.

When studies administering dexamethasone were pooled, 583 deaths were observed (583/2280, 25.6%) in the dexamethasone group compared to 1216 (1216/4494, 27.1%) in the control group. The relative risk was 0.90 (95%CI: 0.83 to 0.98) and the risk difference was -2.83% (95%CI: -5.00% to -0.66%), with the point estimates favoring the use of dexamethasone. The pooled risk difference point estimate was not larger than the -3% minimally clinically important difference, indicating that the point estimate is not clinically relevant. For hydrocortisone, 95 deaths were observed (95/370, 25.7%) compared to 55 (55/188, 29.3%) in the control group. This resulted in a relative risk of 0.84 (95%CI: 0.47 to 1.49) and a risk difference of -3.49 (95%CI: -17.40% to 10.42%). The pooled point estimates favored the use of methylprednisolone. In studies administering methylprednisolone a total of 85 deaths were observed (85/333, 25.5%) in the methylprednisolone group, compared to 100 (100/327, 30.6%) in the control group. This resulted in a pooled relative risk of 0.68 (95%CI: 0.35 to 1.32) and a risk difference of -6.86% (95%CI: -16.88% to 3.17%), where both point estimates favored the use of methylprednisolone. When using a risk difference of 3% as a minimally clinically important difference, the pooled point estimates for hydrocortisone and methylprednisolone show a clinically relevant difference albeit there are wide confidence intervals around these estimates.

Figure 1: Mortality (28-30days) in hospitalized patients.



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval

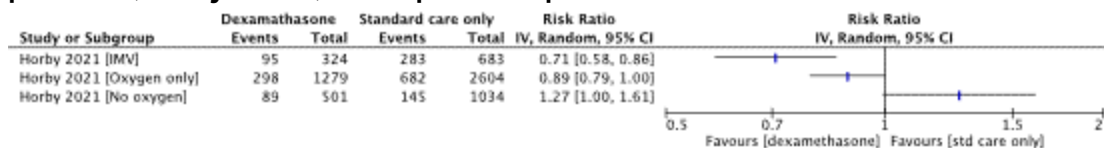
Tomazini (2020) observed 85 death (85/151, 56.3% in the dexamethasone group, compared to 91 death (91/148, 61.5%) in the usual care group. This resulted in a risk difference of -5.2% (95% CI -1.6% to 5.9%). The point estimate favors dexamethasone.

Jamaati (2021) observed 16 deaths (16/25, 64.0%) in the dexamethasone group, while 15 deaths (15/25, 60.0%) were observed in the usual care group. The corresponding risk difference was 4% (95% CI: -22.9% to 30.9%).

Jeronimo (2020) included suspected cases and reported the 7-day mortality (16.5% vs. 23.6%) and 14-day mortality (27.3% vs. 31.7%) in the methylprednisolone vs. placebo groups. On day 28 the mortality increased to 72 observed deaths (72/194, 37.1%) in the methylprednisolone group compared to 76 (76/199, 38.2%) observed deaths in the placebo group. This resulted in a risk difference of -1.1% (95% CI -10.7% to 8.5%), with the point estimates favoring methylprednisolone.

Horby (2021) observed 482 deaths (482/2104, 22.9%) in the dexamethasone group, compared to 1110 deaths (1110/4321, 25.7%) in the usual care group. The corresponding risk difference was -2.8% (95% CI: -5% to -0.6%). Horby (2021) also presented sub-group analyses based on respiratory support status at randomization (see Figure 2). In this figure the risk ratio is depicted, in line with the other studies. The original article displays the rate ratio.

Figure 2: Mortality (day 28) by respiration support status at randomization in hospitalized COVID-19 patients (Horby, 2021) in hospitalized patients.



CI: confidence interval

Angus (2020) observed 41 in-hospital deaths in the fixed-dose hydrocortisone-group (41/137, 30%; RD = -2.8% [95% CI -14.7% to 9.2%]), while in the shock-dependent hydrocortisone-group 37 (37/141, 26%; RD = -6.4% [95% CI -18.1% to 5.3%]) in-hospital deaths were observed compared to 33 deaths (33/101, 32.7%) in the no-hydrocortisone group. Together, 78 deaths occurred (78/278, 28%) in both hydrocortisone groups. In the control group 33 (33/101, 33%) in-hospital deaths occurred (RD = -4.6% [95% CI -15.2% to 6.0%]; favoring hydrocortisone).

Dequin (2020) included both suspected and confirmed cases. Over the course of 21 days, 11 deaths (11/76, 14.5%) were observed in the hydrocortisone-group, compared to 20 deaths (20/73, 27.4%) in the placebo-group. This resulted in a risk difference of -12.9% (95% CI -25.9% to 0.0%), with the point estimate favoring hydrocortisone.

Munch (2021) solely included confirmed cases and reported the all-cause mortality on both day 28 and day 90. Over the course of 28 days, 6 deaths (6/16, 37.5%) were observed in the hydrocortisone-group, compared to 2 deaths (2/14, 14.3%) in the placebo-group. The risk difference was 23.2% (95% CI -6.8% to 53.2%),

favoring placebo. On day 90, the observed deaths increased to 7 (7/16, 44%) and 3 (3/14, 21%), respectively.

Jeronimo (2020) included suspected cases and reported the 7-day mortality (16.5% vs. 23.6%) and 14-day mortality (27.3% vs. 31.7%) in the methylprednisolone vs. placebo groups. On day 28 the mortality increased to 72 observed deaths (72/194, 37.1%) in the methylprednisolone group compared to 76 (76/199, 38.2%) observed deaths in the placebo group. This resulted in a risk difference of -1.1% (95% CI -10.7% to 8.5%), with the point estimates favoring methylprednisolone.

Edalatifard (2020) recruited confirmed cases only and reported the mortality for circa up to 28 days in both groups (approximated from a figure). Two deaths (2/34, 5.9%) were observed in the methylprednisolone group, compared to twelve deaths (12/28, 42.9%) in the standard care-only group. This resulted in a risk difference of -37% (95% CI -56.9% to -17%), with the point estimates favoring methylprednisolone.

Corral-Gudino (2021) recruited confirmed cases only. There were 7 deaths (7/35, 20%) observed in the methylprednisolone group on day 28, compared to 5 (5/29, 17.2%) in the standard care-only group. This resulted in a risk difference of 2.8% (95% CI -16.3% to 21.9%), with the point estimates favoring no methylprednisolone.

Solanich (2021) recruited confirmed cases only. Both COVID-related mortality and all-cause mortality were reported. For COVID-related mortality was reported for day 28 (11.1% vs. 14.3%) and for day 56 (14.8% vs. 14.3%) in the methylprednisolone group vs. standard care-only group, respectively. For the 28-day all-cause mortality, 4 deaths were observed (4/27, 14.8%) in the methylprednisolone group, compared to 6 deaths (6/28, 21.4%) in the standard care-only group. This resulted in a risk difference of -6.6% (95% CI -26.9% to 13.7%), with the point estimates favoring methylprednisolone. At day 56 there were 5 observed deaths (18.5%, methylprednisolone) compared to 6 deaths (21.4%, standard care-only) for mortality.

Tang (2021) recruited confirmed cases only and reported the in-hospital mortality up to 14 days. No deaths were observed in the methylprednisolone group, compared to one death (1/43, 2.3%) in the placebo and standard care group. This resulted in a risk difference of -2.3% (95% CI -16.9% to 3.2%), with the point estimates favoring methylprednisolone.

Systemic corticosteroid use in patients with severe disease

The RECOVERY trial (Horby, 2021), included a subgroup analysis reporting the mortality in patient receiving invasive mechanical ventilation at baseline (IMV, n=1007), see Figure 2. The working group considered this sub-group as having severe disease. The risk difference calculated from the reported events was -12.1% (95% CI -18.3% to -5.9%). This sub-group was furthermore used in the meta-analysis to pool the effect of corticosteroids on mortality in the severe disease group along with the data from Angus (2020) and Tomazini (2020). Figure 3 shows the pooled relative risk in the severe disease group regardless of the type of corticosteroid provided (Angus, 2020; Horby, 2021; Tomazini, 2020). The corresponding pooled risk difference was -9.18% (95% CI: -14.13% to -4.23%), favoring the use of corticosteroids. The pooled point estimate shows a clinically relevant difference.

Figure 3: Mortality in hospitalized patients with severe disease.



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Systemic corticosteroid use in patients with moderate disease

The only RCT including only moderate disease or specifically reporting the moderate disease subgroup seemed to be the RECOVERY trial (Horby, 2021). Here, the mortality was reported in a sub-group of patients receiving oxygen therapy only at randomization while receiving dexamethasone (n=1279) or usual care only (n=2604) during the study period. See Figure 2 for the relative risk in this sub-group. The risk difference was -2.9% (95% CI: -5.8% to -0.0%), indicating with the point estimate that there is no clinically relevant difference.

Systemic corticosteroid use in patients with mild disease

Horby (2021) also presented the results of the sub-group not receiving any oxygen support at randomization in the RECOVERY trial. The working group considered this subgroup as having mild disease. In this sub-group (n=1535) the risk difference calculated from the reported events was 3.7% (95% CI -0.2% to 7.7%), with the point estimate favoring standard care. The point estimate shows a clinically relevant difference. The relative risks of this subgroup receiving no oxygen at randomization is reported in Figure 2. Horby (2021) was the only study that included patients with mild disease.

Level of evidence of the literature

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **mortality (overall)** was downgraded by 1 level due to imprecision (reason: the confidence interval of the pooled risk difference crossed the predefined border of clinical relevance [RD 3% points difference]). We did not downgrade for study limitations (not downgraded for risk of bias: lack of blinding probably does not affect a hard outcome such as mortality). Publication bias was not assessed. The level of evidence for the outcome mortality in hospitalized patients is *moderate*.

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **mortality (severe disease only)** was not downgraded. We did not downgrade for study limitations (not downgraded for risk of bias: lack of blinding probably does not affect a hard outcome such as mortality) and imprecision (reason: using the risks in both groups [34.3% vs 43.7%] and the observed proportion in both groups [$q_1=0.447$, $q_2=0.553$], the calculated needed sample size is $n=897$ [using: $\alpha=0.05$, $\beta=0.2$]). Publication bias was not assessed. The level of evidence for the outcome mortality (severe disease) in hospitalized patients is *high*.

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **mortality (moderate disease only)** was downgraded 1 level due to imprecision (reason: confidence interval of the risk difference crosses the clinical border of 3%). We did not downgrade for study limitations (not downgraded for risk of bias: lack of blinding probably does not affect a hard outcome such as mortality) and publication bias was not assessed. The level of evidence for the outcome

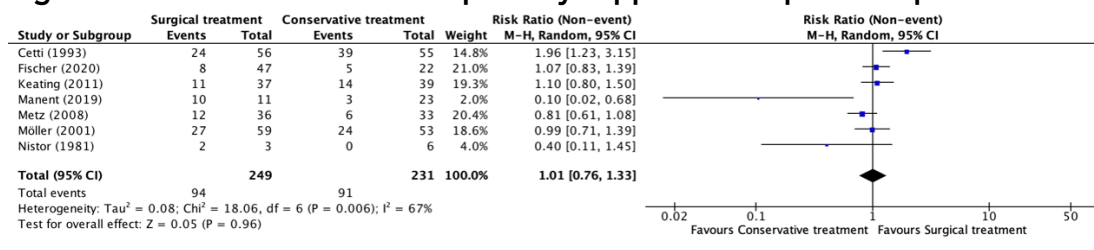
mortality (moderate disease) in hospitalized patients is *moderate*.

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **mortality (mild disease only)** was downgraded by 2 levels due to imprecision (reason: using the risks in both groups [17.8% vs 14.0%] and the 1:2 allocation scheme [$q_1=0.33$, $q_2=0.67$], the calculated needed sample size in the intervention group is $n=1137$ and for the control group $n=2308$ [using: $\alpha=0.05$, $\beta=0.2$]). We did not downgrade for study limitations (not downgraded for risk of bias: lack of blinding probably does not affect a hard outcome such as mortality). Publication bias was not assessed. The level of evidence for the outcome mortality (mild disease) in hospitalized patients is *low*.

Extensive respiratory support

Five RCTs reported the need for extensive respiratory support (Corral-Gudino, 2021; Dequin, 2020; Horby, 2021; Jamaati, 2020; Jeronimo, 2020). Figure 4 shows an overview of the relative risks.

Figure 4: Need for extensive respiratory support in hospitalized patients.



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval; **IV:** Invasive (mechanical) ventilation; **NIV:** Non-invasive ventilation

Tomazini (2020), including confirmed or suspected cases, reported the number of days on mechanical ventilation. The dexamethasone group had a mean duration of 12.5 days (95% CI 11.2 to 13.8) compared to 13.9 days (95% CI 12.7 to 15.1). The adjusted mean difference was -1.54 days (95%CI -3.24 to 0.12, adjusted for age and baseline PaO_2/FiO_2 ratio).

The relative risk from the data reported in Jamaati (2021) was 1.18 (95% CI 0.66 to 2.11) and the risk difference was 8% (95% CI -19.6% to 35.6%) with the point estimate favoring standard care, which is considered a clinically relevant difference. Jamaati (2021) also reported the need for non-invasive mechanical ventilation and observed that 23 patients (23/25, 92%) in the dexamethasone-group and 24 patients (24/25, 96%) in the standard care only-group needed non-invasive ventilation (RR = 0.96, 95% CI 0.83 to 1.10). The risk difference was -4% (95% CI -17.1% to 9.1%), where the point estimate does not indicate a clinically relevant difference.

Horby (2021) included both suspected and confirmed cases resulting in a relative risk of 0.75 (95% CI 0.61 to 0.93) and a risk difference of -2% (95% CI -3.4% to -0.6), with the point estimates favoring dexamethasone while not being considered a clinically relevant difference.

Angus (2020) reported the respiratory support-free days in the sample of both suspected and confirmed cases. The mean adjusted odds ratio in the fixed dose hydrocortisone group compared to the no-

hydrocortisone group was 1.45, with the point estimate favoring hydrocortisone. For the shock dependent hydrocortisone group the mean adjusted odds ratio was 1.31 compared to the no-hydrocortisone group, with the point estimate favoring hydrocortisone.

Dequin (2020) included both suspected and confirmed cases. Respiratory support status on day 21 was reported. In the hydrocortisone group 17 patients (17/76, 22.3%) had mechanical ventilation on day 21, compared to 17 patients (17/73, 23.3%) in the placebo group (RR = 0.96 [95% CI 0.53 to 1.73]; RD = 0.9% [95% CI -14.4% to 12.6%]; favoring hydrocortisone, no clinically relevant difference). High-flow oxygen therapy on day 21 was provided for 3 patients (3/76, 4%) in the hydrocortisone group, while none of the patients received this type of support in the placebo group (RD = 4% [95% CI -1.1% to 9.0%]; favoring placebo, no clinically relevant difference).

Jeronimo (2020) only recruited suspected cases and reported the need for invasive mechanical ventilation until day 7. In the methylprednisolone group, 18 patients (18/93, 19.4%) needed invasive mechanical ventilation, compared to 16 patients (16/95, 16.8%) in the placebo group. The calculated relative risk from this data was 1.15 (95% CI 0.62 to 2.11) and the risk difference was 2.6% (95% CI -7.5% to 14.7%), with the point estimates favoring the placebo group while not indicating a clinically relevant difference.

Edalatifard (2020) recruited confirmed cases only and reported the need for oxygen therapy on day 3. Oxygen therapy was needed in 28 patients (28/34, 82.4%) in the methylprednisolone group versus 26 patients (26/28, 92.8%) in the standard care-only group. The need for oxygen therapy was a composite of the need for nasal cannula, mask oxygen, reservoir mask, non-invasive ventilation, and invasive ventilation. The calculated relative risk from this data was 0.89 (95% CI 0.74 to 1.07) and the risk difference was -10.5% (95% CI -26.5% to 5.5%), with the point estimates favoring the methylprednisolone group and indicating a clinically relevant difference.

Corral-Gudino (2021) reported the progression of respiratory insufficiency which required non-invasive ventilation. Requirement of non-invasive ventilation due to progression was observed in 10 patients (10/35, 28.6%) in the methylprednisolone group compared to 7 patients (7/29, 24.1%) in the standard care-only group. The calculated relative risk from this data was 1.18 (95% CI 0.52 to 2.72) and the risk difference was 4.4% (95% CI -17.2% to 26.0%), with the point estimate favoring the standard-care only group while not indicating a clinical relevant difference.

Solanich (2021) included confirmed cases only and reported the duration of oxygen support, the need for high-flow oxygen or ventilatory support, and the duration of high-flow or ventilatory support. The methylprednisolone group had a median of 11.0 days (IQR: 8.0-19.5) of oxygen support compared to 13 days (IQR: 7.75-23.0) in the standard care-only group. High-flow or ventilatory support was provided to 14 patients in the methylprednisolone group (14/27, 51.9%) versus 18 patients (18/28, 64.3%) in the standard care-only group. The calculated relative risk from this data was 0.81 (95% CI 0.51 to 1.27) and the risk difference was -12.4% (95% CI -38.3% to 13.5%), with the point estimates favoring the methylprednisolone group. The risk difference point estimate indicates a clinically relevant difference. Median duration of high-flow or ventilatory support was 8 days (IQR: 5.0-27.2) in the methylprednisolone group versus a median of 6.5 days (IQR: 4.25-14.20) in the standard care only-group.

Tang (2021) recruited confirmed cases only and reported the need for respiratory support therapies. Patients received high-flow oxygen (4.6% vs. 2.3%), non-invasive positive pressure ventilation (0% vs. 2.3%), invasive mechanical ventilation (4.6% vs. 2.3%), and/or extracorporeal membrane oxygenation (4.6% vs. 0%) in the methylprednisolone group versus the placebo group, respectively.

Level of evidence of the literature

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **extensive respiratory support** was downgraded by 2 levels because of study limitations (1 level for risk of bias, several (potential) flaws in the included studies: lack of blinding of several roles (e.g. open label, or health care providers not blinded), ITT analyses were not followed); number of included patients (1 level for imprecision: relatively small number of patients in the study); publication bias was not assessed. The level of evidence for the outcome respiratory support in hospitalized patients is *low*.

Duration of hospitalization (important)

Horby (2021) found that patients receiving dexamethasone had a shorter length of stay (median of 12 days) compared to patients receiving the usual care only (median of 13 days), however this is not considered to be a clinically relevant difference.

Jamaati (2021) included confirmed SARS-CoV2 cases and found a median duration of hospitalization of 11 days (IQR: 6 to 16) in the dexamethasone-group (n=25) compared to 6 days (IQR: 4 to 9) in the standard care only-group (n=25). In the subgroup that survived, the median duration of hospitalization for the dexamethasone-group (n=9) was 11 days (IQR: 9 to 21) compared to 8.5 days (IQR: 5 to 13) in the standard care only-group (n=10). This was not considered to be a clinically relevant difference.

Angus (2020) reported the hazard ratio of duration of hospitalization in the sample of both suspected and confirmed cases. The median adjusted hazard ratio in the fixed dose hydrocortisone group compared to the control group was 0.97 (95% credible interval: 0.72 to 1.32), with the point estimate favoring hydrocortisone. For the shock dependent hydrocortisone group the median adjusted hazard ratio was 0.93 (95% credible interval: 0.69 to 1.26) compared to the hydrocortisone group, with the point estimate favoring no-hydrocortisone.

Jeronimo (2020) included suspected cases only. The median days of hospitalization was 10 days (IQR 7-13) in the methylprednisolone group. In the placebo group, the median duration of hospitalization was 9 days (IQR: 7-11). No significant ($p=0.296$) and clinically relevant differences between groups were found.

Solanich (2021) included confirmed cases only and observed a median duration of hospitalization of 13 days (IQR: 8.5-21) in the methylprednisolone group, compared to a median of 14 days (IQR: 9-22.5) in the standard care group. No significant ($p=0.933$, Wilcoxon test) and clinically relevant differences between groups were found.

Tang (2021) included confirmed cases only. The median duration of hospitalization was 17 days (IQR: 13-22)

and 13 days (IQR: 10-20) in the methylprednisolone and placebo groups, respectively. No significant differences between groups were found ($p=0.314$, $HR = 1.3$ [95% CI 0.84-2.00]), however the difference in median duration (i.e. 4 days) is considered to be clinically relevant.

Level of evidence of the literature

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **duration of hospitalization** was downgraded by 2 levels because of study limitations (2 levels for risk of bias: potential risk of bias since four trials had no or unclear blinding of health care providers). Publication bias was not assessed. The level of evidence for the outcome respiratory support (need for respiratory support therapies) in hospitalized patients is *low*.

Time to clinical improvement (important)

Solanich (2021) included confirmed cases only and reported the number of patients reaching clinical stability. Here, clinical stability was defined as meeting all 4 criteria for 48 hours: body temperature of 37.5°C or less; PaO_2/FiO_2 ratio over 400 and/or SpO_2/FiO_2 ratio over 300; and a respiratory rate of 24 rpm or less. In the methylprednisolone group 21 patients (21/27, 77.8%) achieved clinical stability at day 56 compared to 22 patients (22/28, 78.6%) in the standard care-only group ($RR = 1.04$, 95% CI 0.38 to 2.82; $RD = 0.8\%$, 95% CI -21.0% to 22.6%; point estimates favour methylprednisolone). Median time to reach clinical stability in the methylprednisolone group was 10 days (IQR: 7-13) versus 11 days (IQR: 8-18.8) in the standard care-only group ($HR = 0.73$, 95% CI 0.39-1.37), which indicates no clinically relevant difference.

Tang (2021) included confirmed cases and reported the number of patients reaching clinical cure. Clinical cure was defined as meeting all of the following criteria: the clinical signs and symptoms of COVID-19 are improved or alleviated (i.e. body temperature for 3 consecutive days, respiratory symptoms improved significantly, CT images showed absorption and/or consolidation of bilateral ground-glass opacification), and no additional treatment was necessary. At day 14 after randomization there were 22 patients (22/43, 51.2%) in the methylprednisolone group achieving clinical cure compared to 25 patients (25/43, 58.1%) in the placebo group ($RR = 1.17$, 95% CI 0.73-1.86; $RD = 7.0\%$, 95% CI -14.0% to 28.0%; point estimates favor placebo). The median time to achieve clinical cure was 14 days (IQR: 10-19) versus 12 days (IQR: 9-17) in the methylprednisolone and placebo groups, respectively ($HR = 1.04$, 95% CI 0.67-1.62), which indicates no clinically relevant difference.

Level of evidence of the literature

The certainty of evidence started as high since the body of evidence consisted solely of RCTs. The level of evidence regarding the outcome measure **time to clinical improvement** was downgraded by 3 levels because of study limitations (1 level for risk of bias: open-label study, lack of blinding of care providers) and number of included patients (2 levels for imprecision: very low number of included patients); Publication bias was not assessed. The level of evidence for the outcome time to clinical improvement in hospitalized patients is *very low*.

Corticosteroids in non-hospitalized COVID-19 patients

No studies were found investigating the effect of corticosteroids in non-hospitalized COVID-19 patients.

Results

No studies were found investigating the effect of corticosteroids on mortality, respiratory support, duration of hospitalization, or time to clinical improvement in non-hospitalized COVID-19 patients.

Level of evidence of the literature

GRADE assessment could not be performed. No studies were found investigating the effect of corticosteroids on mortality, respiratory support, duration of hospitalization, or time to clinical improvement in non-hospitalized COVID-19 patients.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with corticosteroids compared to treatment without corticosteroids in patients with COVID-19?

PICO 1

- P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
- I: systemic corticosteroid use + standard care
- C: standard care only or placebo treatment + standard care
- O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

- P: non-hospitalized patients with COVID-19
- I: systemic corticosteroid use + standard care
- C: standard care only or placebo treatment + standard care
- O: 28-30 day mortality (if not available, any other reports of mortality), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making; and duration of hospitalization, and time to clinical improvement as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support, and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days difference for duration of hospitalization and time to clinical

improvement, and a 5% points absolute difference need for respiratory support and ICU admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were, when possible, categorized based on respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms up to and including 2 September 2021. The detailed search strategy is outlined under the tab Methods. The systematic literature search resulted in 75.172 hits. Studies were selected based on the following criteria: peer-reviewed randomized controlled trials published in an indexed journal, comparing the addition of any non-inhaled corticosteroid to standard care with standard care (whether or not with the addition of a placebo) in patients with COVID-19. Studies investigating inhaled corticosteroids were excluded. Eventually, eleven studies were included.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, eleven RCTs were included in the analysis of the literature concerning hospitalized patients. These studies investigated dexamethasone (n=3), hydrocortisone (n=3), or methylprednisolone (n=5). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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interleukine-6 remmers

Uitgangsvraag

Wat is de plaats van interleukine (IL-)6 remmers bij de behandeling van COVID-19 patiënten?

Aanbeveling

Behandeling IL-6 remmers (in het bijzonder tocilizumab) blijkt met name bij patiënten met progressieve ziekte en een (matig) ernstige respiratoire insufficiëntie, in combinatie met corticosteroïden, een overlevingsvoordeel te bieden. Op basis van het bewijs is het advies:

Behandel opgenomen patiënten met respiratoire klachten door COVID-19 en een toegenomen zuurstofbehoefte met **tocilizumab 600 mg eenmalig i.v.** indien zij reeds zijn gestart met dexamethason **en** een CRP ≥ 75 mg/L hebben **en** een persisterend respiratoire verslechtering leidend tot noodzaak tot hoge zuurstofsuppletie - via een venturimasker (≥ 6 L O₂), non-rebreathing masker, NIV of high flow nasal oxygen (Optiflow) - met als meest aannemelijke verklaring de COVID-19 geïnduceerde longinflammatie (**niet** b.v.: longembolieën of bacteriële pneumonie).

Behandel patiënten met respiratoire insufficiëntie die vanaf de SEH direct op de IC worden opgenomen (en daarom buiten het ziekenhuis al eerder aan de bovengenoemde criteria zouden hebben voldaan) naast dexamethason met tocilizumab. Hierbij wordt geadviseerd de therapie <24 uur na opname op de IC toe te dienen.

Indien tocilizumab niet beschikbaar is of dit om een andere reden niet gegeven kan worden, dan kan andere anti-inflammatoire therapie overwogen worden:

- **baricitinib 4 mg dagelijks gedurende 14 dagen of tot ontslag** of **sarilumab 400 mg eenmalig i.v.** (geen voorkeur uitgesproken voor een van beide middelen)

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder IL-6 remmers bij patiënten met COVID-19. Tot en met 24 januari 2022 werden er 17 gerandomiseerde gecontroleerde studies (RCT's) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=4774 in de interventiegroep en n=4231 in de controlegroep). De meeste RCT's onderzochten het middel tocilizumab (10 studies), daarnaast werd er onderzoek gedaan naar sarilumab (4 studies), levilimab (1 studie). Twee studies randomiseerden naar meerdere IL-6 remmers (tocilizumab of siltuximab en tocilizumab of siltuximab) of de standaardbehandeling. De grootste studie die werd meegenomen was de RECOVERY trial (Horby, 2021), met meer dan 4000 geïnccludeerde patiënten. Er werden alleen studies gevonden die IL-6 remmers onderzochten bij opgenomen patiënten.

De cruciale uitkomstmaten voor de besluitvorming waren mortaliteit en de noodzaak voor uitgebreide respiratoire ondersteuning. De verschillende IL-6 remmers worden apart besproken.

Er werden alleen gerandomiseerde en gecontroleerde trials geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat dat er een aantal open-label trials waren (waaronder de RECOVERY trial), met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten, werd de kwaliteit van dit bewijs waar nodig naar beneden bijgesteld. Daarnaast waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van het betrouwbaarheidsinterval rondom de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs ook naar beneden werd bijgesteld. Er is, waar mogelijk, een sensitiviteitsanalyse gedaan waarin alleen kwalitatief goede studies en studies met meer dan 80% corticosteroiden in de standaard behandeling werden geïnccludeerd.

IL-6 remmers bij patiënten die waren opgenomen in het ziekenhuis

Sinds het begin van de COVID-19 pandemie is IL-6 remming in diverse onderzoeken toegepast in de behandeling van patiënten met COVID-19, met tegenstrijdige resultaten. De data betroffen grotendeels patiënten met redelijke tot ernstige COVID-19. De meeste studies onderzochten de IL-6 remmer tocilizumab. Een gepoolde analyse naar het effect van tocilizumab op de mortaliteit binnen 28 dagen laat met een redelijke zekerheid zien dat er een reductie in de mortaliteit optreedt bij het gebruik tocilizumab (risk ratio: 0,90, 95% CI: 0,83 tot 0,98). Het gepoolde (en gewogen) risicoverschil is echter klein (risicoverschil: -0,01, 95% CI: -0,04 tot 0,02). Echter, in deze resultaten werd de studie van Gordon (2021) niet meegenomen, omdat in deze studie niet de 28 dagen mortaliteit maar de 21 dagen mortaliteit werd gerapporteerd. Daarnaast bevat deze analyse een aantal kwalitatief slechtere studies en studies waarin de standaard behandeling vrijwel geen corticosteroiden bevatte.

Als de studies van Horby (2021), Rosas (2021b) en Gordon (2021) gecombineerd worden (die allen van goede kwaliteit waren en waarin de standaard behandeling in meer dan 80% corticosteroiden bevatte), kan er nog steeds met redelijke zekerheid geconcludeerd worden dat er een significante reductie in de mortaliteit optreedt, echter, het risicoverschil is dan ook klinisch significant (boven de 4% punten, die vooraf gedefinieerd werden als grens voor klinische significantie).

Hier onder zullen wij de verschillen tussen de studies bespreken en bovenstaande resultaten in een context plaatsen.

De 'oudere' studies, die met name in 2020 gepubliceerd werden, toonden wisselende resultaten bij het effect op klinische verbetering. In de CORIMUNO-19 studie (Mariette, 2021) werd aangetoond dat patiënten met tocilizumab minder kans hadden op het gecombineerde eindpunt non-invasieve ventilatie, mechanische ventilatie of overlijden, vergeleken met patiënten die de standaard behandeling ontvingen (24% versus 36%). Deze uitkomst was net statistisch significant ($p=0,04$). In de EMPACTA-studie van Salama (2020) hadden patiënten in de tocilizumab arm minder kans op het gecombineerde eindpunt mechanische ventilatie of overlijden (12,0% vs 19,3%). Effect op klinische verbetering werd echter niet bevestigd in de andere RCT's, waaronder de COVACTA studie (Rosas, 2021a). De tijd tot klinische verbetering, ontslag of stoppen van beademing werd onderzocht in de trial van Stone (2020), deze toonde op al deze punten geen verschil aan tussen de tocilizumab-groep en de groep met standaard behandeling. Ook in de studie van Salama (2020) en Salvarani (2020) was er geen verschil in tijd tot klinische verbetering of ontslag tussen beide groepen. Hierbij moet worden vermeld dat de incidentie van overlijden in het onderzoek van Salvarani (2020), laag was. In deze Italiaanse studie kan dit vermoedelijk verklaard worden door exclusie van patiënten die niet geschikt

waren voor de intensive care in verband met co-morbiditeiten, waardoor er een minder zieke populatie geselecteerd werd. In de COVACTA studie (Rosas, 2021a) was er wel een statistisch significant effect zien in tijd tot ontslag van 20 versus 28 dagen. Op de overige uitkomsten kon ook in deze studie geen effect worden aangetoond. Toepassing van tocilizumab bleek in de bovengenoemde studies relatief veilig.

Een gerandomiseerde open label trial, waarin de effectiviteit van de behandeling met tocilizumab in patiënten met ernstige COVID-19 werd onderzocht (Veiga, 2021), werd voortijdig beëindigd, omdat er op dag 15 na inclusie een hogere sterfte werd gezien in de tocilizumab groep (11 patiënten [17%]) t.o.v. de controlegroep (2 patiënten [3%]). Tevens waren er meer bijwerkingen gezien in de tocilizumab groep (43% versus 34% in de groep met standaardbehandeling). De populatie bestond uit opgenomen patiënten met bevestigde COVID-19 en extra zuurstofbehoefte of mechanische beademing en met ten minste 2 van 4 verhoogde 'biomarkers' (D dimeer, ferritine, CRP en LDH). De auteurs zelf noemen een aantal beperkingen van deze studie: 1) beperkte statistische power (patiënt aantallen in de studie zijn klein), 2) de groepen lijken niet gelijk aan het begin van de behandeling (m.n. zuurstoftoediening en beademing), 3) er is onduidelijk op welk moment de tocilizumab (en andere medicatie) werd toegediend. Slechts 7% van de patiënten kreeg bij aanvang corticosteroiden.

Op basis van bovenstaande studies was er in 2020 geen onderbouwing voor het adviseren van tocilizumab in de behandeling van patiënten met COVID-19. Echter, begin 2021 verscheen de data van 2 grotere gerandomiseerde onderzoeken, die als eerste een evident effect van tocilizumab op de mortaliteit rapporteerden:

Recovery trial

De grootste studie die geïnccludeerd werd, was de RECOVERY trial van Horby (2021). In deze studie werd tocilizumab vergeleken met de standaard behandeling als patiënten voldeden aan de volgende criteria: hypoxie (of $SO_2 < 92\%$ zonder extra O_2 toediening, of noodzaak van O_2 toediening) en $CRP \geq 75$ mg/L. Uiteindelijk werden er 4116 patiënten in deze studie geïnccludeerd, waarvan 562 patiënten (14%) invasief beademend werden. De grote meerderheid (82%) van de patiënten kreeg ook corticosteroiden. Het primaire eindpunt, de 28-dagen sterfte, werd gehaald als volgt: in de tocilizumab groep overleden 621 (31%) patiënten, terwijl in de groep met de standaardbehandeling 729 (35%) patiënten overleden (RR 0,85; 95% CI 0,76-0,94; $p=0,0028$). Het grootste voordeel werd behaald bij die patiënten die ook met corticosteroiden werden behandeld. Ook werden er significante verschillen in de secundaire eindpunten gevonden. Het percentage patiënten dat met tocilizumab werd behandeld en levend na 28 dagen uit het ziekenhuis werd ontslagen was groter, respectievelijk 57% versus 50% (RR 1,22; 95% CI 1,12-1,33; $p<0,0001$). De patiënten die initieel niet beademd werden, hadden een grotere kans om niet aan de beademing komen of te overlijden (35% vs. 42%; risk ratio 0,84; 95% CI 0,77-0,92 $p<0,0001$).

Als de onderzoekspopulatie werd gestratificeerd naar het type ademhalingsondersteuning (enkel toediening van O_2 , niet-invasieve beademing en invasieve beademing), was er in geen van de afzonderlijke strata een statistisch significant verschil tussen tocilizumab en de standaard behandeling wat betreft het relatieve risico op overlijden binnen 28 dagen. Dit houdt verband met de kleinere groepsgrootte per stratum, maar betekent ook dat het advies - ondanks een trend - niet toegespitst kan worden op de benodigde ademhalingsondersteuning.

REMAP-CAP

Een andere grote studie, de REMAP-CAP studie van Gordon (2021), werd niet meegenomen in de gepoolde resultaten van de (28 dagen) mortaliteit in deze richtlijn omdat zij hun uitkomstmaat na 21 dagen rapporteerden. Ook de REMAP-CAP is een multicenter, open label, adaptive platform trial dat onderzoek doet naar patiënten met ernstige pneumonie, binnen of buiten de pandemische setting. Het COVID-19 immuunmodulatie domein bestaat uit 5 armen: IL-6 remmer (tocilizumab), IL-6 remmer (sarilumab), IL-1 receptor antagonist (anakinra), interferon beta-a1 en een controlegroep (geen immuunmodulatie). Aan 353 patiënten werd tocilizumab toegediend, sarilumab werd gegeven aan 48 patiënten in dit domein. Er zijn 402 patiënten in de controlegroep geïnccludeerd. Alle patiënten lagen opgenomen op de intensive care en ontvingen de gift met de IL-6 remmer binnen 24 uur na het starten van orgaanondersteuning. In de groep patiënten met tocilizumab ontving 29% van de patiënten een tweede dosis 12-24u na de eerste gift. De grote meerderheid (80%) van de patiënten kreeg ook dexamethason. De primaire uitkomst was het aantal dagen zonder respiratoire of cardiovasculaire orgaanondersteuning (zogenaamde "organ support free days") binnen 21 dagen na randomisatie. Alle in het ziekenhuis overleden patiënten kregen hierbij de slechtste score (-1). Van de overige patiënten werd berekend hoeveel dagen zonder orgaanondersteuning zij hadden tot 21 dagen. Meer dagen zonder orgaanondersteuning betekent hierbij dus een sneller herstel. Het aantal (mediaan) dagen zonder orgaanondersteuning was 10 (interquartile range [IQR] -1, 16), 11 (IQR 0, 16) en 0 (IQR -1, 15) voor tocilizumab, sarilumab en de controlegroep respectievelijk. De kans op overlijden in het ziekenhuis was 28,0% (98/350) in de tocilizumab groep, 22,2% (10/45) in de sarilumab groep en 35,8% (142/397) in de controle groep. Vergeleken met de controle groep was de mediane adjusted odds ratio voor ziekenhuisoverleving 1,64 (95% CI 1,14; 2,35) voor tocilizumab en 2,01 (95% CI 1,18; 4,71) voor sarilumab.

Sinds het verschijnen van de bovenstaande grote RCT's, zijn er twee kleinere onderzoeken gepubliceerd die geen effect van IL-6 remmers laten zien op de mortaliteit na 28 dagen of progressie van de ziekte. De studie van Rosas (2021b) includeerde patiënten met een matige en ernstige COVID-19 pneumonie, maar hield geen rekening met inflammatie bij inclusie. De studie van Sancho-Lopez (2021) includeerde patiënten met een matig-ernstig ziektebeeld, maar mogelijk minder inflammatie dan in de REMAP-CAP studie. Daarnaast werden corticosteroïden korter gegeven in de andere studies (minimaal 3 dagen methylprednisolon). Mogelijk verklaren deze verschillen het ontbreken van een aantoonbaar effect van IL-6 remming.

Bij het formuleren van een advies over tocilizumab is het belangrijk om niet alleen naar de 28 dagen mortaliteit te kijken, omdat studies die andere uitkomstmaten rapporteren (zoals Gordon, 2021) dan niet meegenomen kunnen worden. Ook representeren de meer recente RCT's waarschijnlijk beter de huidige situatie, waarin corticosteroïden deel uitmaken van de standaardbehandeling.

Als alle bovenstaande overwegingen worden meegenomen, kunnen we de volgende conclusie trekken over het effect van tocilizumab: er is een statistisch significant voordeel te zien van tocilizumab op de mortaliteit, de omvang van het effect is in de twee grootste geïnccludeerde studies ook ruim boven de vooraf gestelde definitie van klinische significantie (4% verschil in 28 dagen mortaliteit bij Horby, 2021; 8% verschil in 21 dagen mortaliteit bij Gordon, 2021). Dit effect lijkt bij zowel matig zieke patiënten met inflammatie (een veel gebruikt inclusiecriteria) als bij ernstig zieke patiënten aanwezig te zijn. Ook op de andere uitkomstmaten 'extensive respiratory support' en 'opnameduur' zijn er voordelen zichtbaar van tocilizumab, al zijn deze niet altijd even groot en statistisch significant.

Soort IL-6 remmer

Verreweg de meeste studies bestudeerden tocilizumab als IL-6 remmer. Sarilumab werd vier studies bestudeerd, met relatief kleine aantallen patiënten. De resultaten van deze studies lijken ook op een mogelijk voordeel te wijzen van sarilumab. Echter, door onder andere de beperkte power van deze studies zijn de resultaten niet significant. Sarilumab werd in de REMAP-CAP studie toegediend als intraveneuze infusie van 400 mg. Er zijn alleen preparaten voor subcutane injectie in Nederland geregistreerd. Uit deze subcutane formulering kan een intraveneuze toediening worden klaargemaakt conform protocol van REMAP-CAP. Tocilizumab is wel als intraveneuze infusie in Nederland geregistreerd, waardoor intraveneuze toediening conform het label kan plaatsvinden. Bovendien is, zowel binnen als buiten dit studieverband, meer ervaring met het gebruik van tocilizumab. Om deze redenen is er bij voldoende beschikbaarheid een voorkeur voor het gebruik van tocilizumab. Bij onvoldoende beschikbaarheid van tocilizumab is toediening van sarilumab intraveneus (uit de subcutane formulering) een optie.

Dosering

Tocilizumab wordt in alle genoemde studies gedoseerd op basis van gewicht. De meeste studies houden een schema aan van 8 mg/kg met een maximum van 800 mg per dag. De RECOVERY studie doseerde volgens gewichtsklassen, waarbij de doseringen tocilizumab werden afgerond. Patiënten van 40-65 kg kreeg 400 mg, patiënten van 65-90 kg kregen 600 mg, en patiënten van >90 kg kregen 800 mg tocilizumab. Dit heeft als voordelen dat het gemakkelijker te doseren is met minder kans op toedienfouten en minder spillage. Het toedienen van tocilizumab in een 'fixed-dose' regime zou dus meer voordelen kunnen hebben, maar tot voor kort waren er geen gegevens beschikbaar over de farmacokinetiek van tocilizumab bij patiënten met ernstige COVID-19. Moes (2021) beschrijft deze farmacokinetiek in een artikel. In 139 plasma monsters van 29 IC patiënten werd de concentratie tocilizumab geanalyseerd en gemodelleerd. De uitkomst was dat tocilizumab doseren op basis van gewicht (8 mg/kg) leidt tot grotere variabiliteit in de gemeten spiegels. De minimaal benodigde plasmaconcentratie voor het behoud van maximale IL-6-receptorbezetting (5 µg/ml) wordt echter bij alle patiënten voor ten minste 15 dagen behouden, onafhankelijk van dosering o.b.v. gewicht. Uit de simulaties wordt duidelijk dat een 'fixed-dose' van 600 mg voor alle IC-patiënten minder variatie in blootstelling geeft, en wel de benodigde plasmaconcentratie behaalt en behoudt.

De patiëntenpopulatie met een indicatie voor het gebruik van tocilizumab op de verpleegafdeling en op de IC liggen dusdanig in elkaars verlengde dat hierin eenzelfde advies gevolgd kan worden. Als dosering wordt geadviseerd om tocilizumab in een 'fixed-dose' van 600 mg toe te dienen (en is een klinisch gelijk effect te verwachten als bij een dosering van 8 mg/kg). Het is ook mogelijk om het doseerschema van de RECOVERY studie te volgen voor patiënten opgenomen op de verpleegafdeling, maar zal leiden tot meer spillage:

- 40-65 kg: 400 mg tocilizumab
- 65-90 kg: 600 mg tocilizumab
- >90 kg: 800 mg tocilizumab

Sarilumab kan gegeven worden in 400 mg intraveneus eenmalig conform het protocol van REMAP-CAP.

Alternatieve, lagere dosering van tocilizumab bij (dreigend) ernstig tekort aan IL-6 remmers

In de klinische gerandomiseerde studies werd tot heden een dosis tocilizumab gebruikt die ook geregistreerd is voor de behandeling van reumatologische aandoeningen. Een duidelijke rationale voor de initiële keuze van deze dosis voor de specifieke behandeling van COVID-19 ontbrak. In een artikel van Moes (2021) wordt de farmacokinetiek van tocilizumab in patiënten met COVID-19 die op de intensive care afdeling waren opgenomen, beschreven. Hieruit bleek o.a. dat een lagere éénmaal daags gegeven dosis van 400 mg in

plaats van 600 mg volgens modelering leidt tot een beperkt verlies van het aantal dagen dat de concentratie tocilizumab zich boven de gestelde doelconcentratie bevindt (plusminus 16.5 versus 19 dagen). Het is onbekend of dit ook leidt tot een relevante afname van het klinisch effect. Op grond van de beschikbare gegevens lijkt het onwaarschijnlijk, dat een potentieel verlies van effect evenredig is aan de dosisverlaging van 600 naar 400 mg.

Om deze reden kan, indien noodzakelijk, bij een (dreigend) tekort aan tocilizumab en afwezige beschikbaarheid van geschikte formuleringen van andere IL-6 remmers, tijdelijk worden overgegaan op een lagere eenmalige vaste dosis van 400 mg tocilizumab i.v., **of** een begin dosis van 200 mg iv gevolgd door een 2^e dosis van 200 mg na 7 dagen.

Tweede dosering

In de tocilizumab groep van beide studies (REMAP-CAP en RECOVERY) ontving ongeveer een derde van de patiënten een tweede dosis 12-24u na de eerste dosis op basis van inzichten van de behandelend arts. Het is niet duidelijk wat de criteria voor een tweede toediening zijn geweest. Ook is nog niet helder of er verschil van effect is bij een eenmalige versus tweevoudige gift. Tevens is het ook o.b.v. pathofysiologische en farmacologische overwegingen twijfelachtig of herhaalde toediening toegevoegde waarde zouden kunnen hebben. Vooralsnog is er daarom onvoldoende onderbouwing om een tweede gift te adviseren.

IL-6-remmers en zwangerschap en kinderen

Tocilizumab is het eerste keus middel voor de behandeling van COVID-19 positieve zwangere of lacterende vrouwen indien zij volgens de SWAB leidraad voor anti-IL-6 therapie in aanmerking komen. De indicatiestelling en dosering van tocilizumab gebeurt idealiter in multidisciplinair teamverband waarvan tenminste een longarts en/of internist en/of intensivist en perinatoloog deel uit moeten maken. Alhoewel zwangere en lacterende vrouwen ondervertegenwoordigd waren in studies, zijn er op dit moment geen aanwijzingen dat tocilizumab teratogeen of foetotoxisch is (Jorgenson, 2021). De excretie van tocilizumab in moedermelk is laag. Als tocilizumab niet beschikbaar is, kan overwogen worden om sarilumab te geven, echter, de ervaring met sarilumab gebruik in de zwangerschap is zeer beperkt. Na toediening van elke immuunmodulator in de zwangerschap in verband met COVID-19, zoals tocilizumab en sarilumab, dient kort na de geboorte een kinderarts in consult gevraagd te worden, ook al vindt de bevalling niet direct plaats. Na het gebruik van tocilizumab en sarilumab moet een bloedbeeld worden bepaald bij de neonat, omdat infectiediagnostiek bij de neonat minder goed te interpreteren kan zijn. Ook worden vaccinaties bij de neonat met een levend virus in het eerste levensjaar afgeraden.

Bij kinderen is er geen bewijs dat COVID-19 met meer complicaties gepaard gaat, de ziekte lijkt bij kinderen juist met minder complicaties gepaard te gaan. Dat zou pleiten voor terughoudendheid voor het voorschrijven van IL-6 remmers bij minder zieke pediatrische patiënten (niet op IC opgenomen).

Overige overwegingen

Door gebruik van IL-6 remmers wordt de productie van CRP gedurende 14-28 dagen geremd (dieptepunt van CRP-productie ligt meestal tussen dag 7-15). Het CRP is derhalve geen biomarker meer voor (verdenking op) infecties. Het is mogelijk dat er minder CRP-gestuurde interventies plaatsvonden in de interventie groepen.

Mogelijk zou de meting van procalcitonine (PCT) minder onderdrukt worden door IL-6 remmers, maar studies zijn hierover niet eenduidig.

Bijwerkingen

Een Cochrane review uit 2021 beschrijft niet alleen de effectiviteit van tocilizumab bij COVID-19, maar ook data over de veiligheid (Ghosn, 2021). Zij beschrijven 7 RCT's waarin niet significant vaker 'adverse events' worden gezien, vergeleken met de controlegroep (RR 1,23, 95%CI 0,87-1,72). Echter, deze conclusie heeft een bewijskracht van 'zeer laag'.

Ook bij inflammatoire ziekten zoals reumatoïde artritis is er ervaring met tocilizumab. 'Adverse events' die in deze setting werden beschreven zijn onder andere een verhoogd risico op infecties (bij met name bovenste luchtwegen), leverenzymstoornissen, neutropenie en trombocytopenie, hyperlipedemie en gastrointestinale symptomen (Schoels, 2012). Deze werden 1,2 maal vaker gezien dan in de controlegroep (Singh, 2010). In deze setting wordt tocilizumab echter vaak langdurig gegeven. 'Adverse events' zijn dan ook niet zonder meer te extrapoleren naar de behandeling van COVID-19, waarbij er een eenmalige gift wordt gegeven.

Virusvarianten

Sinds de opkomst van de omikron variant van SARS-CoV-2 in Nederland eind 2021, is de kans op een ernstig beloop van COVID-19 op populatieniveau zeer sterk gedaald. Het is van belang om op te merken dat de besproken gerandomiseerde studies werden verricht voor de opkomst van de omikron variant. Het is onduidelijk wat de invloed is van deze variant op het effect van anti-inflammatoire therapie, al wordt aangenomen dat patiënten die door de omikron variant een ernstige COVID-19 infectie ontwikkelen nog steeds baat hebben bij anti-inflammatoire therapie. De 'number needed to treat' zou wel anders (vermoedelijk hoger) kunnen zijn.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens kunnen IL-6 remmers worden ingezet in de behandeling van COVID-19. In de behandeling van COVID-19, waar deze middelen relatief kortdurend worden voorgeschreven, werden voordelen van IL-6 remmers gevonden (zoals een lagere mortaliteit), maar werden niet meer bijwerkingen gezien. Mogelijk zijn de patiënten aantallen nog niet groot genoeg om alle bijwerkingen in de behandeling van COVID-19 aan te tonen. Een potentieel verhoogd risico op infecties of andere bijwerkingen die bij de behandeling van bijvoorbeeld reumatoïde artritis gezien werden, moet dus meegewogen worden in de keuze om een patiënt met een IL-6 remmer te behandelen. Deze potentiële bijwerkingen spelen overigens ook een rol bij andere anti-inflammatoire middelen die ingezet kunnen worden bij COVID-19.

Kosten (middelenbeslag)

In de huidige studies varieert de gebruikte IL-6 remmer en ook de dosering varieert. De dosering tocilizumab die aanbevolen wordt in deze richtlijn is gebaseerd op gewicht. Indien er 600mg tocilizumab wordt voorgeschreven, dan kost dit rond de 1000 euro. Hierin zijn niet de opname in het ziekenhuis of andere bijkomende kosten meegenomen.

Aanvaardbaarheid, haalbaarheid en implementatie

Op grond van de bekende onderzoeksgegevens kunnen IL-6 remmers worden ingezet in de behandeling van COVID-19. Tocilizumab is beschikbaar in Nederland en patiënten die in aanmerking komen voor deze behandeling liggen opgenomen in het ziekenhuis. De werkgroep voorziet geen problemen qua implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Interleukine-6 remmers blijken met name bij patiënten met progressieve ziekte en een (matig) ernstige respiratoire insufficiëntie, in combinatie met corticosteroïden, een overlevingsvoordeel te bieden. Een tijdige start van deze geneesmiddelen (zoals in de REMAP-CAP studie) lijkt van belang.

Het brede inclusie criterium zoals gebruikt in de RECOVERY studie was: progressieve ziekte en een hypoxemie ($\text{SpO}_2 < 92\%$ zonder extra O_2 toediening, of met noodzaak van O_2 toediening), en een $\text{CRP} \geq 75 \text{ mg/L}$. Dit kan bij toepassing in de praktijk tot verwarring leiden. Vanwege deze reden heeft de commissie dit gegeven om praktische redenen vertaald naar de noodzaak tot het gebruik van $\geq 6 \text{ L O}_2$. Dit is in de kliniek tevens de overgang van zuurstoftoediening via een neusslang naar een z.g.n. venturimasker, non-rebreathing masker, NIV of high flow nasal oxygen (Optiflow), en voorkomt waarschijnlijk het onnodig gebruik van tocilizumab bij een mildere vorm van de ziekte.

In bovengenoemde patiënten populatie met (matig) ernstige COVID-19, zorgen niet alleen IL-6 remmers (in het bijzonder tocilizumab), maar ook JAK remmers (in het bijzonder baricitinib) voor een klinisch relevante afname van de mortaliteit binnen 28 dagen vergeleken met placebobehandeling. Van beide soorten middelen beschrijven RCT's geen significante bijwerkingen, al betreft dit een relatief korte follow-up.

Het verwachte effect en de bewijskracht van de literatuur betreffende het effect van tocilizumab en baricitinib op mortaliteit is vergelijkbaar, vooral als er niet alleen gekeken wordt naar de 28 dagen mortaliteit maar ook andere follow-up duur. Er is meer ervaring met tocilizumab in de behandeling van COVID-19 in Nederland en dit middel werd in grotere aantallen patiënten onderzocht: 12 RCT's onderzochten bij ruim 7000 patiënten het effect van tocilizumab, Ter vergelijking: 3 RCT's onderzochten bij ruim 2500 patiënten baricitinib. In patiënten met een (matig) ernstige COVID-19 infectie wordt er daarom een voorkeur uitgesproken voor tocilizumab.

Advies:

Behandel opgenomen patiënten met respiratoire klachten door COVID-19 en een toegenomen zuurstofbehoefte met **tocilizumab 600 mg eenmalig i.v.** indien zij reeds zijn gestart met dexamethason **en** een $\text{CRP} \geq 75 \text{ mg/L}$ hebben **en** een persisterend respiratoire verslechtering leidend tot noodzaak tot hoge zuurstofsuppletie - via een venturimasker ($\geq 6 \text{ L O}_2$), non-rebreathing masker, NIV of high flow nasal oxygen (Optiflow) - met als meest aannemelijke verklaring de COVID-19 geïnduceerde longinflammatie (**niet** b.v.: longembolieën of bacteriële pneumonie).

Behandel patiënten met respiratoire insufficiëntie die vanaf de SEH direct op de IC worden opgenomen (en daarom buiten het ziekenhuis al eerder aan de bovengenoemde criteria zouden hebben voldaan) naast dexamethason met **tocilizumab**. Hierbij wordt geadviseerd de therapie <24 uur na opname op de IC toe te dienen.

Indien tocilizumab niet beschikbaar is of dit om een andere reden niet gegeven kan worden, dan kan andere anti-inflammatoire therapie overwogen worden:

- **baricitinib 4 mg dagelijks gedurende 14 dagen of tot ontslag of sarilumab 400 mg eenmalig i.v.**
(geen voorkeur uitgesproken voor een van beide middelen)

Voor de behandeling van kinderen kunnen de doseringen beschreven in het Kinderformularium worden gebruikt.

Onderbouwing

Achtergrond

Een infectie met SARS-CoV-2 kan leiden tot ernstige pneumonie en ARDS. De term *cytokine storm* werd genoemd bij COVID-19 in relatie tot dysregulatie van de immuunrespons. Dit zou wijzen op een verhoging van pro-inflammatoire cytokines, zoals interleukine (IL-)6. IL-6 remmers (b.v. tocilizumab) zijn al geregistreerd voor het *cytokine release syndrome* dat kan ontstaan ten gevolge van immunotherapie met Chimere Antigeen Receptor (CAR) T-cel therapie. Het toedienen van IL-6 remmers lijkt daarmee een potentiële therapie voor patiënten met COVID-19 en verhoogde IL-6 waarden. Hoewel de IL-6 concentraties bij COVID-19 patiënten verhoogd zijn, zijn deze waarden 10 tot 40 maal lager dan bij patiënten met ARDS (Sinha, 2020; Kox, 2020). Het is lastig om IL-6 waarden te vergelijken, omdat er verschillende bepalingsmethoden zijn die niet goed zijn gestandaardiseerd. Een mogelijk additioneel effect van anti-IL-6 therapie naast anti-inflammatoir effect is remming van de coagulatie-activatie bij COVID-19 (Levi, 2020).

Inmiddels hebben diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit van IL-6 remmers onderzocht om de plaats van deze middelen bij de behandeling van COVID-19 patiënten te bepalen. Klinische dose-finding studies zijn in deze setting nooit verricht. De groep IL-6 remmers bevat zowel monokloale antistoffen gericht tegen de IL-6 receptor (tocilizumab, sarilumab, levilimab) als anti-IL6 monoklonale antistoffen (siltuximab).

Conclusies / Summary of Findings

Mortality (crucial) – Tocilizumab

Moderate GRADE	<i>Based on high quality studies AND studies with more than 80% use of corticosteroids in the standard of care:</i> Treatment with tocilizumab probably reduces mortality when compared with treatment without tocilizumab in <u>hospitalized</u> patients with (moderate and severe) COVID-19. <i>Source: Hermine, 2020; Gordon, 2021; Horby, 2021; Rosas, 2021a.</i>
<i>Mortality (crucial) in other IL-6 inhibitors than tocilizumab</i>	
Low GRADE	<i>Based on high quality studies AND studies with more than 80% use of corticosteroids in the standard of care:</i> Treatment with sarilumab probably reduces mortality when compared with treatment without sarilumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Gordon, 2021; Sancho-Lopéz, 2021.</i>
Low GRADE	Treatment with sarilumab may result in little to no clinically relevant difference in mortality when compared with treatment without sarilumab in <u>hospitalized</u> patients with <u>moderate</u> COVID-19. <i>Source: Lescure, 2021; Mariette, 2021; Sancho-Lopéz, 2021.</i>
Moderate GRADE	Treatment with sarilumab probably reduces mortality when compared with treatment without sarilumab in <u>hospitalized</u> patients with <u>severe</u> COVID-19. <i>Source: Gordon, 2021; Lescure, 2021.</i>
- GRADE	No evidence was found regarding the effect of treatment with levilimab on mortality when compared with treatment without levilimab in <u>hospitalized</u> patients with COVID-19. <i>Sources: none.</i>
Very low GRADE	The evidence is very uncertain about the effect of treatment with siltuximab on mortality when compared with treatment without siltuximab in <u>hospitalized</u> patients with COVID-19. <i>Sources: Declercq, 2021.</i>

Extensive respiratory support (crucial)

Low GRADE	Treatment with tocilizumab may result in little to no difference in need for extensive respiratory support when compared with treatment without tocilizumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Gordon, 2021; Hermine, 2020; Horby, 2021; Rosas, 2021; Salama, 2021; Salvarani, 2020; Soin, 2021; Stone, 2020; Veiga, 2021.</i>
<i>Extensive respiratory support (crucial) in other IL-6 inhibitors than tocilizumab</i>	
Very low GRADE	The evidence is very uncertain about the effect of treatment with sarilumab in need for extensive respiratory support when compared with treatment without sarilumab in <u>hospitalized</u> patients with COVID-19. <i>Sources: Gordon, 2021; Lescure, 2021; Mariette, 2021; Merchante, 2021; Sancho-Lopéz, 2021.</i>
- GRADE	No evidence was found regarding the effect of treatment with levilimab in need for extensive respiratory support when compared with treatment without levilimab in <u>hospitalized</u> patients with COVID-19. <i>Sources: none.</i>
Very low GRADE	Evidence is very uncertain about the effect of treatment with tocilizumab or siltuximab in need for extensive respiratory support when compared with treatment without tocilizumab or siltuximab in <u>hospitalized</u> patients with COVID-19. <i>Sources: Declercq, 2021</i>

Duration of hospitalization (important)

Low GRADE	Treatment with tocilizumab may result in a reduced length of stay compared with treatment without tocilizumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Gordon, 2021; Hermine, 2020; Horby, 2021; Rosas, 2021a; Rosas, 2021b; Salama, 2021; Salvarani, 2020; Soin, 2021; Stone, 2020; Veiga, 2021; Wang, 2021.</i>
<i>Duration of hospitalization (important) in other IL-6 inhibitors than tocilizumab</i>	
Low GRADE	Treatment with sarilumab may result in a reduced length of stay when compared with treatment without sarilumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Lescure, 2021; Mariette, 2021; Merchante, 2021; Sancho-Lopéz, 2021.</i>
Low GRADE	Treatment with levilimab may result in little to no difference of length of stay when compared with treatment without levilimab in <u>hospitalized</u> patients with COVID-19. <i>Source: Lomakin, 2021.</i>
Very low GRADE	Evidence is very uncertain about the effect of treatment with tocilizumab or siltuximab on length of stay when compared with treatment without tocilizumab or siltuximab in <u>hospitalized</u> patients with COVID-19. <i>Source: Declercq, 2021.</i>

Time to clinical improvement (important)

Low GRADE	Treatment with tocilizumab may result in little to no difference in time to clinical improvement when compared with treatment without tocilizumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Salama, 2021; Soin, 2021; Stone, 2020; Wang, 2021.</i>
<i>Time to clinical improvement (important) in other IL-6 inhibitors than tocilizumab</i>	
Moderate GRADE	Treatment with sarilumab probably results in little to no difference in time to clinical improvement when compared with treatment without sarilumab in <u>hospitalized</u> patients with COVID-19. <i>Source: Lescure, 2021.</i>
- GRADE	No evidence was found regarding the effect of treatment with levilimab on time to clinical improvement when compared with treatment without levilimab in <u>hospitalized</u> patients with COVID-19. <i>Source: none.</i>
Very low GRADE	Evidence is very uncertain about the effect of treatment with tocilizumab or siltuximab on time to clinical improvement when compared with treatment without tocilizumab or siltuximab in <u>hospitalized</u> patients with COVID-19. <i>Source: Declercq, 2021.</i>

Samenvatting literatuur

Description of studies

IL-6 INHIBITORS

Declercq (2021) (COV-AID) reported a multicentre (n=16), open label, randomised controlled phase 3 trial in Belgium. Declercq (2021) aimed to assess whether tocilizumab, siltuximab or anakinra shortened the time to clinical improvement in patients with COVID-19. Patients were eligible for randomization if they met the inclusion criteria (e.g., PaO₂/FiO₂ < 350 mmHg on room temperature or < 280 mmHg on supplemental oxygen and bilateral pulmonary infiltrates; use invasive mechanical ventilation, OR non-invasive ventilation or continuous use of CPAP for hypoxia, OR oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system). In total 342 patients were randomly assigned to treatment with anakinra and standard care (n=112) or only standard care (n=230), and simultaneously randomly assigned to IL-6 blockade (n=227; 114 for tocilizumab and n=113 for siltuximab) or no IL-6 blockade (n=115). Therefore, 44 patients received only anakinra, 32 patients received anakinra + tocilizumab, 36 patients received anakinra + siltuximab, 81 patients received only tocilizumab, 75 patients received only siltuximab, and 74 patients received only standard care. Most patients received hydroxychloroquine (i.e., 42% assigned before August 2020) or dexamethasone (i.e., 84% assigned from August 2020; steroids were used in 60% of the total patient population) as standard care. The median (IQR) age was 65 (54-73) years in the intervention group (i.e., IL-6 blockade group), compared with 64 (55-72) in the control group (i.e., no IL-6 blockade group). In the

intervention group 175/227 (77.1%) were males, compared with 90/115 (78.3%) in the control group. The length of the follow-up was 28 days. The following relevant outcome measures were included; duration of hospitalization, time to clinical improvement, respiratory support. The primary outcome was time to clinical improvement. This resulted in a median (range) of 11 days (10-16) in the intervention group, compared with 12 days (11-16) in the control group, HR: 1.00 (95%CI 0.78 to 1.29). There are some concerns regarding risk of bias as the study had an open label design.

Gordon (2021) (REMAP-CAP trial) describes the results of, an international, multifactorial, adaptive platform trial, comparing tocilizumab (n=353) or sarilumab (n=48) in combination with standard of care to standard of care alone (n=402, control group). However, this article is a preliminary report. For this literature summary, the results of sarilumab intervention group and the control group were used. The study included critically ill patients with COVID-19 admitted to ICU and receiving respiratory or cardiovascular organ support. Patients required high-flow nasal cannula, non-invasive ventilation or invasive mechanical ventilation. In total 865 patients were included. The mean (SD) age was 61.4 (12.7) years, and 629/865 (72.7%) of them were males. Patients in the intervention group received sarilumab 400mg (n=48) or tocilizumab (n=353), both in addition to standard care (i.e., no protocol, depending on site, glucocorticoids were used in 93% of the patients). Patients were mostly treated with COVID-19 Immunoglobulin, COVID-19 antiviral, therapeutic anticoagulation, and corticoids at baseline. The control group (n=402) received only standard care. The length of the follow-up was 90 days. The following relevant outcome measures were included; mortality (i.e., in hospital death), duration of hospitalization, need for respiratory support, any serious adverse events. The primary outcome was the number of respiratory and cardiovascular organ support-free days up to day 21. This resulted in a median (IQR) of 11 (0 to 16) days/ 10 (-1 to 16) days in the intervention groups (i.e., sarilumab/tocilizumab), compared with 0 (-1 to 15) days in the control group. There are some concerns regarding risk of bias as the current study had an open-label design.

LEVILIMAB

Lomakin (2021) (CORONA) described a phase III, double-blind, placebo-controlled, randomized trial, which was conducted at 12 hospitals in the Russian Federation. Lomakin (2021) evaluated the efficacy and safety of IL-6 inhibitor levilimab in combination with standard care, compared with only standard care in patients with severe COVID-19. Standard care was in accordance with the National clinical guidelines of the Ministry of Health of the Russian Federation, which included symptomatic treatment, antiviral agents, anticoagulants, supportive care, etc. Hydroxychloroquine, antithrombotic agents, macrolides and lincosamides were mostly used as concomitant therapy. In total 206 patients met the in- and exclusion criteria and were randomized. The mean (SD) age was 59 (13) years in the intervention group (n=103), compared with 58 (11) years in the control group (n=103). In the intervention group 58/103 (56.3%) were males, compared with 51/103 (49.5%) in the control group. The length of the follow-up was 60 days. The following relevant outcome measures were included; mortality, duration of hospitalization, safety. The primary outcome was the proportion of patients with sustained clinical improvement on day 14. This was achieved in 65/103 (63.1%) patients in the intervention group, compared with 44/103 (42.7%) patient in the control group (difference: 20.4%). There are no concerns regarding risk of bias.

Note: The initial primary endpoint was the overall mortality, but the observed mortality rate in the study population was significantly lower than the assumed value. Thus, the study had not enough power to detect the difference between the groups using overall mortality. Therefore, the primary endpoint changed.

SARILUMAB

Lescure (2021) (Sarilumab COVID-19 Global Study Group) described a phase 3, double-blind placebo-controlled, multicenter randomized controlled trial. Lescure (2021) evaluated the clinical efficacy and safety of sarilumab (200 mg or 400mg) in addition to standard of care versus standard of care alone in patients admitted to the hospital with COVID-19 with indication of oxygen or ventilation support. In total 416 patients were included. The median (range) age was 59 (50-68) years, and 216/416 (51.9%) of them were males. Intervention group I (n=159) received sarilumab 200mg, and intervention group II (n=173) received sarilumab 400mg. The control group (n=84) received placebo. All patients received stand care, which included corticosteroids at randomisation in 20%. The length of the follow-up was 60 days. The following relevant outcome measures were included; mortality (i.e., patients alive at day 29), duration of hospitalization (i.e., number of days of hospitalization among patients alive at day 60), time to clinical improvement, need for respiratory support. In the current summary of literature intervention group II (i.e., sarilumab 400mg) was labelled as 'intervention group, and intervention group I (i.e., sarilumab 200mg) was labelled as 'intervention group 200mg'. The primary endpoint was time to clinical improvement of two or more points (i.e., estimated based on Kaplan-Meier). This resulted in a median (IQR) 10 (9 to 12) days in intervention group I, 10 (9 to 13) days in intervention group II, and 12 (9 to 15) days in the control group. The HR were 1.03 (95%CI 0.75 to 1.40), and 1.14 (95%CI 0.84 to 1.54), respectively for I-I vs. placebo and II-I vs. placebo.

Mariette (2021) (CORIMUNO-19-SARI-1 Collaborative Group) reported resulted of a multicentre (n=6, France), open-label, randomised controlled phase 2/3 trial, nested within the CORIMUNO-19 cohort. Mariette (2021) assessed the ability of sarilumab to improve the outcome of patients hospitalised with COVID-19 pneumonia. Eligible patients (n=148) were randomized to treatment with sarilumab and standard care (i.e., antibiotic agents, antiviral agents, corticosteroids (15% and 25% of the patients in the intervention and the control group, respectively, were treated with corticosteroids), vasopressor support, anticoagulants at the discretion of the clinicians) or only standard care. Of them, 68 were randomized to the intervention group, and 80 to the control group. In the intervention group, 35/68 (51.4%) received a second injection of sarilumab. Four patients in the control group withdrew consent, and therefore 76 patients were included in the analyses. The median (IQR) age in the intervention group was 62 (53-71) years, compared with 63 (26-72) in the control group. In the intervention group 49/68 (72.1%) were males, compared with 59/76 (77.6%) in the control group. The length of the follow-up was 90 days, and no patients were lost to follow-up. The following relevant outcome measures were included; mortality at day 28 and day 90, duration of hospitalisation, respiratory support, safety. The study reported 2 primary outcomes; proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (i.e., 18/68 (26%) patients in the intervention group vs. 20/76 (26%) controls), and survival with no need for mechanical or non-invasive ventilation at day 14 (i.e., 25/68 (37%) patients in the intervention group vs. 26/76 (34%) controls). Importantly the current study was stopped early as no (positive) clinical effect was shown at the interim analysis.

Merchante (2021) (SARICOR) reported resulted of a multicentre (n=10, Spain), open-label, randomised controlled phase 2 trial. Merchante (2021) investigate the efficacy and safety of early treatment with sarilumab in patients hospitalised with COVID-19 pneumonia. Eligible patients (n=115) were randomized to treatment with sarilumab (200mg or 400mg) and standard care (i.e., according to local practice; dexamethasone was used in 90% of the included patients) or only standard care. Of them, 37 were randomized to intervention

group I (i.e., sarilumab 200mg), 39 to intervention group II (i.e., 400mg sarilumab), and 39 to the control group. One patient in intervention group I and one patient in intervention group II withdrew consent. The median (IQR) age was 59 (51-70) years, and 78/115 (67.8%) of the patients were males. The length of the follow-up was 28 days, and no patients were lost to follow-up. The following relevant outcome measures were included; mortality at day 28, respiratory support, duration of hospitalisation, need for ICU admission, and time to clinical improvement. The primary outcome was defined as the development of ARDS requiring HFNO, NIMV or IMV during the first 28 days after randomization. This was observed in 10/37 (27.0%) patients in intervention group I, 10/39 (25.6%) patients in intervention group II, and 5/39 (12.8%) in the control group. The HR were 0.87 (95%CI 0.37 to 2.06), and 0.41 (95%CI 0.14 to 1.18), respectively for I-I vs. placebo and II-I vs. placebo. There are some concerns regarding risk of bias as the current study had an open-label design.

Sancho-Lopéz (2021) (SARTRE) reported results of an open-label randomized controlled trial performed in 8 tertiary hospitals in Spain. Sancho-Lopéz (2021) evaluated the clinical efficacy of sarilumab in addition to standard of care versus standard of care alone in patients admitted to the hospital with COVID-19 requiring supplemental oxygen by mask or nasal prongs. Glucocorticoids were given to all patients at a 1 mg/kg/day of methylprednisolone for at least 3 days. In total 201 patients were included. Of them 99 were randomized to the intervention group (i.e., addition of sarilumab (IV) at a single dose), and 102 to the control group. The mean (SD) age in the intervention group was 60 (11.5) years, and 60 (11.8) years in the control group. In the intervention group 71/99 (71.7%) were males, compared to 70/102 (68.6%) in the control group. The length of the follow-up was 28 days. The following relevant outcome measures were included; mortality at day 28, duration of hospitalization (i.e., time to hospital discharge), need for respiratory support, any (serious) adverse events. The primary outcome was the proportion of patients progressing to severe respiratory failure. This was observed in 16/99 (16.2%) patients in the intervention group, compared with 16/102 (15.7%) patient in the control group. This resulted in a RR of 1.03 (95%CI 0.48 to 2.20). There are some concerns regarding risk of bias as the current study had an open-label design.

TOCILIZUMAB

Hermine (2020) (CORIMUNO-19-TOCI-1 trial) compared outcomes of tocilizumab in combination with usual care (n=64) with best supportive care (n=67) in a cohort-embedded multicenter open-label Bayesian RCT in nine university hospitals in France. Hospitalized patients were included with moderate or severe COVID-19 pneumonia and oxygen requirement but not admitted to the intensive care unit. Patients did not require high-flow oxygen by nasal cannula, non-invasive ventilation, or mechanical ventilation (World Health Organization clinical progression scale [WHO-CPS] score of 5). Patients in the tocilizumab group received intravenously administration of tocilizumab of 8 mg/kg on day 1. Administration of an additional fixed dose of tocilizumab, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician. Usual care (antibiotic agents, antiviral agents, corticosteroids (16% and 18% of the patients in the intervention and the control group, respectively, were treated with corticosteroids prior to randomisation, 30% and 55% respectively after randomisation.), vasopressor support, anticoagulants) was provided at the discretion of the clinicians. The length of follow-up was 28 days. Primary outcomes were scores higher than 5 on the World Health Organization 10-point Clinical Progression Scale (WHO-CPS) on day 4 and survival

without need of ventilation (including non-invasive ventilation) at day 14. In the tocilizumab group, 12 patients had a WHO-CPS score greater than 5 at day 4 compared to 19 in the control group (median posterior absolute risk difference [ARD] -9.0% ; 90% credible interval [CrI], -21.0 to 3.1). At day 14, 12% (95%CI -28% to 4%) fewer patients needed non-invasive ventilation (NIV) or mechanical ventilation (MV) or died in the tocilizumab group than in the control group (24% versus 36%, median posterior HR 0.58; 90% CrI, 0.33 to 1.00).

Horby (2021) (RECOVERY trial) describes the results of the RECOVERY trial, a large open-label trial investigating the effect of multiple drug treatment. The trial was conducted in 131 National Health Service Hospitals in the UK. At first randomization, patients were randomized to usual care or usual care plus either lopinavir–ritonavir, dexamethasone, hydroxychloroquine or azithromycin. For the current study, patients were randomized at a second randomization to receive either tocilizumab and usual care ($n=2022$) or usual care alone ($n=2094$). Patients were hospitalized patients with clinical evidence of progressive COVID-19, indicated by an oxygen saturation $< 92\%$ on room air or receiving oxygen therapy, and CRP ≥ 75 mg/L. Of all patients at baseline, 45% received no supplemental oxygen or low-flow oxygen, 41% received high-flow nasal oxygen, continuous positive airway pressure, or other non-invasive ventilation and 14% received invasive mechanical ventilation or ECMO.

Patients in the tocilizumab group received a single intravenous infusion over 60 min. The dose was established by bodyweight and a second dose could be given after 12 to 24 hours if the patient's condition had not improved. Usual care was provided as the standard of care in the participating hospital. At least 82% of the patients received dexamethasone as part of the usual care. The length of follow-up was 28 days. The primary outcome was 28-day mortality. Overall, 621 (31%) of the 2022 patients allocated tocilizumab and 729 (35%) of the 2094 patients allocated to usual care died within 28 days (RR 0.85; 95% CI 0.76 to 0.94).

Rosas (2021a) (COVACTA trial) conducted a phase 3, international, randomized, double-blind, placebo-controlled trial to assess the efficacy and safety of tocilizumab ($n=294$) versus placebo ($n=144$) in hospitalized adult patients with severe COVID-19. Eligible patients were randomly assigned to receive a single intravenous infusion of tocilizumab (at a dose of 8 mg/kg, with a maximum dose of 800 mg) or placebo plus standard care. If clinical signs or symptoms did not improve or worsened, a second infusion of tocilizumab or placebo could be administered 8 to 24 hours after the first dose. Standard care according to local practice (antiviral treatment, low-dose glucocorticoids (used at baseline in 19% of the intervention group and 29% of the placebo group; used during the study in 34% and 52% respectively), convalescent plasma, and supportive care) was provided. However, concomitant treatment with another investigational agent (except antiviral drugs) or any immunomodulatory agent was prohibited. The primary efficacy outcome was clinical status at day 28. Key secondary efficacy outcomes were clinical status at day 14 on the ordinal scale, mortality at day 28, number of ventilator-free days by day 28, the time to improvement from baseline by at least two categories on the ordinal scale, and the time to hospital discharge or readiness for discharge. The median value for clinical status on the ordinal scale at day 28 was 1.0 (95% CI 1.0 to 1.0) in the tocilizumab group and 2.0 (non-ICU hospitalization without supplemental oxygen) (95% CI 1.0 to 4.0) in the placebo group (between-group difference, -1.0 ; 95% CI -2.5 to 0).

Rosas (2021b) (REMDACTA trial) conducted a randomized, double-blind, placebo-controlled, multicenter,

phase 3 trial, evaluated the efficacy and safety of tocilizumab plus remdesivir versus placebo plus remdesivir in patients aged 12 years and older hospitalized with severe COVID-19 pneumonia. Eligible patients were randomly assigned to receive treatment with tocilizumab plus remdesivir (n=430) or placebo plus remdesivir (n=210). Remdesivir was administered intravenously, followed by a single intravenous dose of tocilizumab 8 mg/kg (maximum, 800 mg) or placebo on day 1. Patients with sustained fever or clinically significant worsening of signs and symptoms of COVID-19 (e.g., increased supplemental oxygen requirement) could receive a second infusion of blinded tocilizumab or placebo within 8 to 24 h of the first infusion. Before randomization, about 19% of the patients in both groups received remdesivir. Corticosteroids were part of the standard of care in most patients (83% of the intervention group and 86% of the placebo group used corticosteroids). At baseline, all patients required >6 L/min supplemental oxygen. Patients were monitored through day 60, and the primary end point (time to hospital discharge or "ready for discharge") was assessed at day 28. Secondary outcomes include time from randomization to mechanical ventilation or death, clinical status on the ordinal scale at day 14, and time to death. Median time from randomization to hospital discharge or "ready for discharge" was 14 (95% CI 12 to 15) days with tocilizumab plus remdesivir and 14 (95% CI 11 to 16) days with placebo plus remdesivir (Cox proportional HR 0.97 (95% CI 0.78 to 1.19)).

Salama (2020) (EMPACTA trial) describes an international double-blind, placebo-controlled RCT, comparing the effect of tocilizumab (n = 249) with placebo (n = 128) in hospitalized patients with mild to severe COVID-19. Eligible patients were randomly assigned to receive one or two doses of intravenous tocilizumab (8 mg per kilogram of body weight, to a maximum of 800 mg per dose) or placebo plus standard care. Standard of care was provided according to local practice, which could include antiviral treatment, the limited use of systemic glucocorticoids (recommended dose, ≤ 1 mg per kilogram of body weight of methylprednisolone or equivalent), and supportive care. In total, 80% of the intervention group and 88% of the control group used corticosteroids in the 7 days before or during the trial (duration not specified). Patients that required mechanical ventilation were not eligible for study participation. At baseline, the majority of the patients received supplemental oxygen (64.2%), some received NIV or high-flow oxygen (26.5%) and a minority did not receive any supplemental oxygen (9.3%). The length of follow-up was 60 days. The primary outcome was mechanical ventilation or death by day 28. The cumulative percentage of patients who had received mechanical ventilation or who had died by day 28 was 12.0% (95% CI 8.5 to 16.9) in the tocilizumab group and 19.3% (95% CI, 13.3 to 27.4) in the placebo group (HR 0.56; 95% CI 0.33 to 0.97).

Salvarani (2020) (RCT-TCZ-COVID-19 trial) conducted a prospective, open-label RCT to evaluate the effect of early tocilizumab administration (n=60) versus standard therapy (n=66) in preventing clinical worsening in patients hospitalized with COVID-19 pneumonia in 24 hospitals in Italy. Eligible patients were randomly assigned to receive intravenous tocilizumab (within 8 hours from randomization (8mg/kg up to a maximum of 800mg, followed by a second dose after 12 hours) or standard of care. Patients in the control arm received supportive care following the protocols of each clinical center. All drugs were allowed but IL-1 blockers, Jak inhibitors, and tumor necrosis factor inhibitors. Steroids were allowed if already taken before hospitalization (<10% of the patients). Patients at enrolment were allowed to receive oxygen therapy with Venturi mask or high-flow nasal cannula with recorded and present Fio₂, but not invasive or non-invasive mechanical ventilation and were not admitted to the intensive care unit. However, patients that were admitted to the ICU were not eligible for study participation. In case of occurrence of documented clinical worsening, patients randomized in both arms could receive any therapy, including steroids (<10% of the

patients), and, for patients randomized in the control arm, tocilizumab. The length of follow-up was 14 days for the primary end point (clinical worsening) and 30 days for other outcomes. The primary composite outcome was defined as entry into the intensive care unit with invasive mechanical ventilation, death from all causes, or clinical aggravation documented by the finding of a PaO₂/FIO₂ ratio less than 150mmHg, whichever came first. In total, 17 of 60 patients (28.3%) in the tocilizumab group and 17 of 63 (27.0%) in the control group showed

clinical worsening within 14 days since randomization (RR 1.05; 95%CI, 0.59 to 1.86).

Two patients in the tocilizumab group and 1 in the control group died before 30 days from randomization, and 6 and 5 patients were intubated in the 2 groups, respectively. The trial was prematurely interrupted after an interim analysis for futility.

Soin (2021) (COVINTOC trial) conducted a phase 3, open-label, multicenter, randomized controlled trial to assess the efficacy and safety of tocilizumab plus standard care (n=90) versus standard care alone (n=90) in hospitalized patients with moderate to severe disease. Eligible patients from 12 public and private hospitals across India were randomly assigned to receive a single intravenous tocilizumab infusion at 6 mg/kg up to a maximum dose of 480 mg or standard care. For patients in the intervention group, an additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose. Standard care was provided according to the protocols at the individual study sites. Standard care included corticosteroids in 91% of the patients. At baseline, 81/91 (89.0%) in the intervention group and 80/88 (90.9%) in the control group received supplemental oxygen and 5/91 (5.5%) in the intervention group and 5/88 (5.6%) in the control group received mechanical ventilation. Supplemental oxygen was recommended to treat hypoxia, and high-flow nasal cannula, non-invasive ventilation, and mechanical ventilation could be considered if hypoxia and respiratory distress progressed. The length of follow-up was 30 days. The primary endpoint was progression of COVID-19 (from moderate to severe or from severe to death) up to day 14. Progression of COVID-19 occurred in eight (8.8%) of 91 patients in the tocilizumab group and 11 (12.5%) of 88 in control group (difference -3.71; 95% CI -18.23 to 11.19).

Stone (2020) (BACC Bay Tocilizumab Trial) performed a randomized, double-blind, placebo-controlled trial to assess the efficacy of tocilizumab plus standard care (n=161) versus placebo plus standard care (n=81) in hospitalized patients with confirmed SARS-CoV-2 infection hyperinflammatory states, and at least two of the following signs: fever (body temperature >38°C), pulmonary infiltrates, or the need for supplemental oxygen in order to maintain an oxygen saturation greater than 92%. Eligible patients from seven Boston hospitals were randomly assigned to receive standard care plus a single dose of either tocilizumab (8 mg per kilogram of body weight administered intravenously, not to exceed 800 mg) or placebo. Antiviral therapy, hydroxychloroquine and steroids were permitted as concomitant therapy. Standard care included corticosteroids in 11% of the intervention group and 6% of the placebo group. Data from patients who were event-free at the end of follow-up were censored at 28 days (for intubation (or death, for patients who died before intubation) and clinical worsening) or at 29 days (for discontinuation of supplemental oxygen among patients who had been receiving it at baseline). Data from patients who could not be reached for 28-day follow-up were censored at hospital discharge. The primary outcome was intubation or death. The HR for intubation or death in the tocilizumab group as compared with the control group was 0.83 (95% CI 0.38 to 1.81).

Veiga (2021) (COVID-19 Coalition Brazil VI (TOCIBRAS)) conducted a multicentre, randomised, open label, parallel group, superiority trial to assess the efficacy of tocilizumab plus standard (n=65) versus standard care alone (n=64) in hospitalized patients with severe or critical coronavirus disease and were receiving supplemental oxygen to maintain oxygen saturation greater than 93% or had been receiving mechanical ventilation for less than 24 hours before analysis. Eligible patients from nine hospitals across Brazil were randomly assigned to receive a single intravenous dose of tocilizumab (8 mg/kg, with a maximum of 800 mg) or standard care alone. The concomitant use of hydroxychloroquine, azithromycin, corticosteroids (69% of the intervention and 73% of the control group used corticosteroids during the study), and antibiotics was allowed according to standard care per local institutional guidelines for patients with covid-19. Remdesivir was not available in Brazil. At baseline, more patients in the tocilizumab group than control group were using supplementary oxygen at enrolment (60% vs 44%), whereas use of non-invasive ventilation or high flow oxygen through a nasal cannula was higher in the control group than in the tocilizumab group (23% vs 41%). The follow-up was 15 days for the primary outcome and 29 days for secondary outcomes. The primary outcome was clinical status at 15 days. This was analyzed as a composite of death or mechanical ventilation because the assumption of odds proportionality was not met. In total, 18 of 65 (28%) patients in the tocilizumab group and 13 of 64 (20%) in the control group were receiving mechanical ventilation or died at day 15 (OR 1.54; 95% CI 0.66 to 3.66). Death at 15 control group (OR 6.42; 95% CI 1.59 to 43.2). The data monitoring committee recommended stopping the trial early, after 129 patients had been enrolled, because of an increased number of deaths at 15 days in the tocilizumab group.

Wang (2021) conducted a randomized, controlled, open-label, multicenter trial to assess efficacy and safety of tocilizumab in addition to standard care (n=34) versus standard care alone (n=31) in hospitalized patients with moderate or severe COVID-19. Eligible patients were randomly assigned to receive tocilizumab (400 mg, diluted in 100 mL of 0.9% saline, and administered intravenously for more than 1 h. A second dose was given if a patient remained febrile for 24 h after the first dose) or standard care alone. Standard care was given in accordance with the "Diagnosis and Treatment Protocol for Novel Coronavirus Pneumonia (5th or updated version)" and included corticosteroids in 11%. One patient in the control group that worsened on day 3 after randomization was crossed over to the tocilizumab group. The follow-up was 14 days. The primary end point was the cure rate of the enrolled patients. The cure rate in the tocilizumab group (94.1%) was higher than in the control group (87.1%) (rate difference 95% CI 7.2% to 21.2%).

Table 1. Overview of RCTs comparing IL6-inhibitors with standard care in hospitalized COVID-19 patients.

First author, year	Disease severity, based on need for respiratory support*	Sample size	Intervention
Tocilizumab			

Declercq (2021)	Mixed: mild, moderate and severe disease	I: N=227 (n=114 for tocilizumab and n=113 for siltuximab) C: N=115 Total: N=342	First patients were randomly assigned to receive an IL-1 blockade or not. Thereafter they were randomized to receive an IL-6 blockade or not. -for the second randomization, a subgroup received siltuximab (11 mg/kg i.v. (single injection)) OR tocilizumab (8 mg/kg i.v. (not exceeding 800 mg; single injection))
Gordon (2021)	Severe disease	I: 353 C: 402** Total N=755	One dose of 8 mg tocilizumab per kilogram of actual body weight (up to a maximum of 800 mg) administered IV over period of 1 hour. Dose could be repeated 12 to 24 hours later at the discretion of the treating clinician.
Hermine (2020)	Moderate disease	I: 63 C: 67 Total N=130	Intravenously administration of tocilizumab of 8 mg/kg on day 1. Administration of an additional fixed dose of tocilizumab, 400 mg IV, on day 3 was recommended if oxygen requirement was not decreased by more than 50%, but decision was left to the treating physician.
Horby (2021)	Mixed: mild, moderate and severe disease Mortality stratified for respiratory support at baseline	I: 2022 C: 2094 Total N=4116	A single intravenous infusion of tocilizumab over 60 min was provided. The dose was established by bodyweight (800 mg if weight >90 kg; 600 mg if weight >65 and ≤90 kg; 400 mg if weight >40 and ≤65 kg; and 8 mg/kg if weight ≤40 kg). A second dose could be given 12–24 h later if the patient's condition had not improved.
Rosas (2021a)	Mixed: mild, moderate and severe disease	I: 294 C: 144 Total N=438	A single intravenous infusion of tocilizumab (at a dose of 8 mg per kilogram of body weight, with a maximum dose of 800 mg)

Rosas (2021b)	Mixed: moderate and severe disease	I: 430 C: 210 Total N=640	A single intravenous dose of tocilizumab 8 mg/kg (maximum, 800 mg). Patients with sustained fever or clinically significant worsening of signs and symptoms of COVID-19 (e.g., increased supplemental oxygen requirement) could receive a second infusion tocilizumab within 8 to 24 h of the first infusion.
Salama (2021)	Mixed: mild, moderate and severe disease; not mechanically ventilated	I: 249 C: 128 Total N=377	One or two doses of intravenous tocilizumab (8 mg per kilogram of body weight, to a maximum of 800 mg per dose)
Salvarani (2020)	Mixed: mild, moderate and severe disease	I: 60 C: 66 Total N=126	Tocilizumab intravenously within 8 hours from randomization at a dose of 8 mg/kg up to a maximum of 800 mg, followed by a second dose after 12 hours.
Soin (2021)	Mixed: mild, moderate and severe disease	I: 90 C: 90 Total N=180	Tocilizumab was administered as a single intravenous infusion at 6 mg/kg up to a maximum dose of 480 mg. An additional dose of 6 mg/kg (max 480 mg/kg) could be administered if clinical symptoms worsened or did not show improvement within 12 h to 7 days after administration of the first dose.
Stone (2020)	Mixed: mild, moderate and severe disease	I: 161 C: 81 Total N=242	Tocilizumab (8 mg per kilogram of body weight administered intravenously, not to exceed 800 mg)
Veiga (2021)	Mixed: moderate and severe	I: 65 C: 64 Total N=129	A single intravenous dose of tocilizumab (8 mg/kg, with a maximum of 800 mg)
Wang (2021)	Mixed: moderate and severe	I: 34 C: 31 Total N=65	The first dose of tocilizumab was 400 mg, diluted in 100 mL of 0.9% saline, and administered intravenously for more than 1 h. A second dose was given if a patient remained febrile for 24 h after the first dose.
Sarilumab			
Gordon (2021)	Severe disease**	I: 48 C: 402** Total: 450	Sarilumab, at a dose of 400 mg, was administered as an intravenous infusion once only.

Lescure (2021)	Mixed: the majority of the patients had a moderate disease severity (60%), 40% had severe disease severity.	I-I: N=159 I-II: N=173 C: N=84 Total: N=416	The hospital pharmacist added the contents of prefilled syringes of sarilumab 200 mg solution for subcutaneous injection supplied by the sponsor into a specified volume of locally sourced 0.9% sodium chloride solution for IV infusion (two syringes for the 400 mg dose, one syringe for the 200mg dose).
Mariette (2021)	Moderate: receiving supplemental oxygen without ventilation assistance.	I: 68 C: 76 Total: 144	Sarilumab (IV) at a single dose of 400mg. If an additional dose of 400mg was recommended if oxygen requirement had not decreased by more than 50%.
Merchante (2021)	Mixed: The majority of the patients needed administration of oxygen at baseline. - no oxygen; n=11 - nasal cannula; n= 79 - non-rebreather face mask; n=7 - rebreather face mask; n=18	I-I: 37 I-II: 39 C: 39 Total: 115	I-I: Sarilumab (IV) at a single dose of 200mg. I-II: Sarilumab (IV) at a single dose of 400mg.
Sancho-Lopéz (2021)	Moderate: requiring supplemental oxygen by mask or nasal prongs	I: 99 C:102 Total: 201	Sarilumab (IV) at a single dose of 200 mg for patients <75 kg body weight, or 400 mg for patients weighing ≥75 kg.
Levilimab			
Lomakin (2021)	Mixed: 39% did not require oxygen therapy, 60% require oxygen therapy, 1% require high-flow oxygen therapy or non-invasive ventilation	I: 103 C: 103 Total: 206	Patients allocated to the active drug received a single dose of levilimab at day 1. Levilimab 324 mg administration was performed as two SC injections of 162 mg.
Siltuximab			

Declercq (2021)	Mixed: The majority of the patients needed administration of oxygen at baseline. <i>Intervention:</i> - no oxygen; N=1 - requiring supplemental oxygen; N=50 - on non-invasive ventilation or high flow oxygen devices; N=44 - on invasive mechanical ventilation; N=17 <i>Control:</i> - no oxygen; N=5 - requiring supplemental oxygen; N=119 - on non-invasive ventilation or high flow oxygen devices; N=84 - on invasive mechanical ventilation; N=22	I: N=227 C: N=115 Total: N=342	First patients were randomly assigned to receive an IL-1 blockade or not. Thereafter they were randomized to receive an IL-6 blockade or not. - for the second randomization, a subgroup received siltuximab (11 mg/kg i.v. (single injection)) OR tocilizumab (8 mg/kg i.v. (not exceeding 800 mg; single injection))

****2/402 patients in the control group had none or supplementary oxygen only.**

***Disease severity categories:**

- *mild disease (no supplemental oxygen);*
- *moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);*
- *severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).*

N: Total sample size; I: Intervention; C: Control

Results – IL-6 inhibitors

Since the number of studies that was available and the number of patients that were included, was relatively large, we report all outcomes stratified for the different IL-6 inhibitors. Also conclusions were formulated separately for the different IL-6 inhibitors: i.e. conclusions were reported for tocilizumab and sarilumab, instead of all IL-6 inhibitors combined.

Since the quality of the studies was variable and the use of corticosteroids as part of the standard of care varied from <10% to >90%, the committee decided to conduct and report a sensitivity analysis for the crucial outcomes ('mortality' and 'extensive respiratory support').

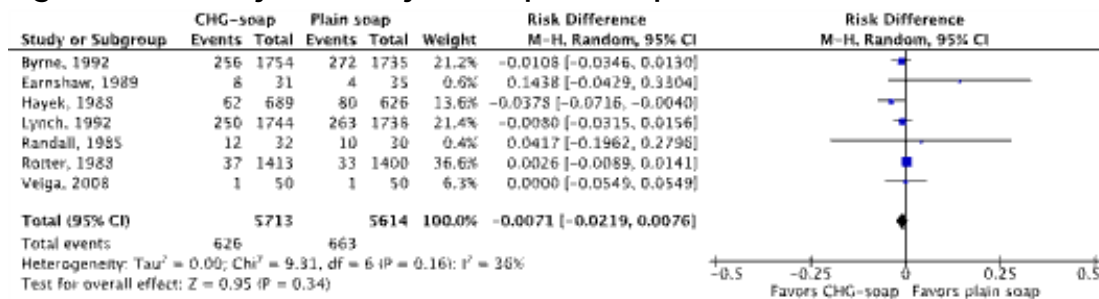
Mortality (crucial)

Results - Tocilizumab

mortality at day 21 – 30

Ten studies reported on the outcome measure mortality at day 21 – 30. The pooled incidence was 927/3785 (24.5%) in the tocilizumab group compared to 987/3336 (29.6%) in the control group. The pooled RR from these ten studies was 0.89 (95% CI 0.82 to 0.96; Figure 1), in favour of the tocilizumab group. The pooled RD was -0.01 (95%CI -0.04 to 0.02). This, *including patients with different disease severity states*, is not considered clinically relevant. Regarding the sensitivity analysis (Figure 1), the pooled RR in the high quality studies AND studies with more than 80% use of corticosteroids in the standard of care, was 0.87 (95%CI 0.80 to 0.94), and the RD was -0.04 (95%CI -0.07 to -0.02). This is considered clinically relevant. The pooled RR in studies with lower quality and/or initiating less than 80% corticosteroids was 1.09 (95%CI 0.83 to 1.43), and the RD was 0.02 (95%CI -0.01 to 0.04). This is not considered clinically relevant.

Figure 1. Mortality 21-30 days in hospitalized patients treated with tocilizumab

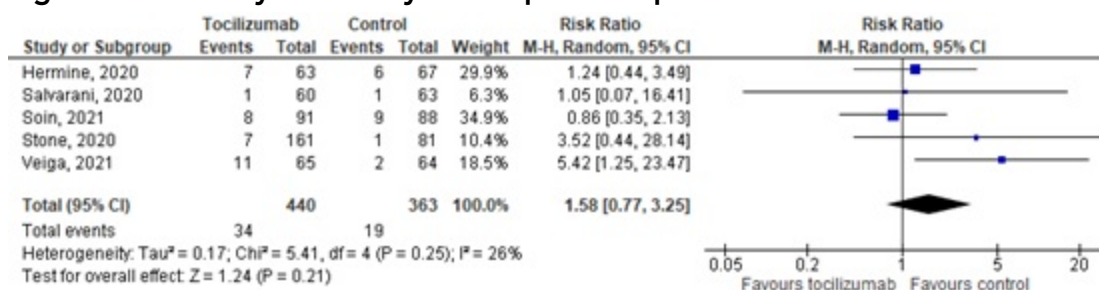


Z: p-value of overall effect; **df:** degrees of freedom; **?**: statistical heterogeneity; **CI:** confidence interval.

mortality at day 14 – 15

Four studies (Hermine, 2020; Salvarani, 2020; Soin, 2021; Stone, 2020) reported on mortality at day 14 and one study (Veiga, 2021) reported on mortality at day 15. The pooled incidence of these five studies was 23/375 (6.1%) in the intervention group compared to 17/299 (5.7%) in the control group. The pooled RR from these studies was 1.58 (95% CI 0.77 to 3.25; Figure 2), in favour of the control group. The pooled RD was 0.027 (95% CI -0.013 to 0.067). This is not considered clinically relevant. Patients included in this analysis had a *mixed* disease state (i.e., mild, moderate or severe). Regarding the sensitivity analysis, all included studies in this analysis were of low quality and/or used <80% corticosteroids.

Figure 2. Mortality 14-15 days in hospitalized patients treated with tocilizumab



Z: p-value of overall effect; **df:** degrees of freedom; **?**: statistical heterogeneity; **CI:** confidence interval.

mortality at day 60

Salama (2021) and Rosas (2021b) reported on mortality at day 60. The pooled mortality rate was 126 out of 680 (18.5%) in the intervention group compared to 69 out of 337 (20.5%) in the control group. The RR is 0.90

(95% CI 0.69 to 1.16). The RD was -0.02 (95% CI -0.07 to 0.03). This is not considered clinically relevant. Patients included in this analysis had a *mixed* disease state (i.e., mild, moderate or severe). Declercq (2021) reported the number of deaths in the subgroups at follow-up (i.e., 10-20 weeks). The incidence of mortality was 10/81 (12.3%) in patients treated with only additional tocilizumab, compared with 9/74 (12.2%) in the control group (i.e., receiving only usual care according to the randomizations). This resulted in a RR of 1.02 (95%CI 0.44 to 2.36) and a RD of 0.00 (95%CI -0.10 to 0.11). This is not considered clinically relevant. Patients included in this analysis had a *mixed* disease state (i.e., mild, moderate or severe). Regarding the sensitivity analysis, all included studies in this analysis were of low quality and/or used <80% corticosteroids.

If possible stratified analyses were performed per disease severity state, see Figure 3.

Moderate disease

Hermine (2020) reported mortality at day 28 – 30 specifically for patients with a moderate disease state. The incidence of mortality was 7/63 (11.1%) in the intervention group, compared with 11/67 (16.4%) in the control group. The RR was 0.68 (95%CI 0.28 to 1.64). The RD was -0.05 (95%CI -0.17 to 0.06). This is considered clinically relevant.

Horby (2021) reported mortality at 28 days specifically for patients with a moderate disease state (e.g., nine patients not receiving any oxygen and 1859 patients receiving simple oxygen only). The incidence of mortality was 180/935 (19.3%) in the intervention group, compared with 214/933 (22.9%) in the control group. The RR was 0.84 (95%CI 0.70 to 1.00). The RD was -0.04 (95CI -0.07 to 0.00). This is considered clinically relevant.

Rosas (2021a) reported mortality at 28 days specifically for patients with a moderate disease state (i.e., patients who received oxygen at baseline but were not mechanically ventilated). The incidence of mortality was 21/183 (14.8%) in the intervention group, compared with 15/90 (16.7%) in the control group. The RR was 0.69 (95%CI 0.37 to 1.27). The RD was -0.05 (95%CI -0.14 to 0.04). This is considered clinically relevant.

The pooled RR in patients with a moderate disease state was 0.82 (95%CI 0.70 to 0.97), and the RD was -0.04 (95%CI -0.07 to -0.01) for mortality at day 28. This is considered clinically relevant.

Severe disease

Horby (2021) reported mortality at 28 days specifically for patients with a severe disease state (e.g., non-invasive ventilation (including high-flow nasal oxygen, continuous positive airway pressure ventilation, and other non-invasive ventilation); and invasive mechanical ventilation (including invasive mechanical ventilation and extracorporeal membranous oxygenation)). The incidence of mortality was 441/1087 (40.6%) in the intervention group, compared with 515/1161 (44.4%) in the control group. The RR was 0.91 (95%CI 0.83 to 1.01). The RD was -0.04 (95%CI -0.08 to 0.00). This is considered clinically relevant.

Rosas (2021a) reported mortality at 28 days specifically for patients with a severe disease state (e.g., patients who were mechanically ventilated at randomization). The incidence of mortality was 31/111 (27.9%) in the intervention group, compared with 19/54 (35.2%) in the control group. The RR was 0.79 (95%CI 0.50 to 1.27). The RD was -0.07 (95%CI -0.22 to 0.08). This is considered clinically relevant.

In addition, Gordon (2021) reported mortality at day 21 in patients with *severe* disease state. The mortality rate was 98 out of 350 (28.0%) in the intervention group compared to 142 out of 397 (35.8%) in the control group. The RR is 0.78 (95% CI 0.63 to 0.97). The RD was -0.08 (95% CI -0.14 to -0.01). This is considered clinically relevant.

The pooled RR in patients with a severe disease state was 0.89 (95%CI 0.81 to 0.97), and the RD was -0.05 (95%CI -0.08 to -0.02) for mortality at day 21-30. This is considered clinically relevant.

Mixed – moderate & severe disease

Rosas (2021b) reported mortality at 28 days specifically for patients with a moderate or severe disease state. The incidence of mortality was 78/430 (18.1%) in the intervention group, compared with 41/210 (19.5%) in the control group. The RR was 0.79 (95%CI 0.50 to 1.27). The RD was -0.01 (95%CI -0.08 to 0.12). This is not considered clinically relevant.

Veiga (2021) reported mortality at 28 days specifically for patients with a moderate or severe disease state. The incidence of mortality was 14/65 (21.5%) in the intervention group, compared with 6/64 (9.4%) in the control group. The RR was 0.79 (95%CI 0.50 to 1.27). The RD was 0.12 (95%CI -0.00 to 0.24). This is considered clinically relevant (*in favour of control*).

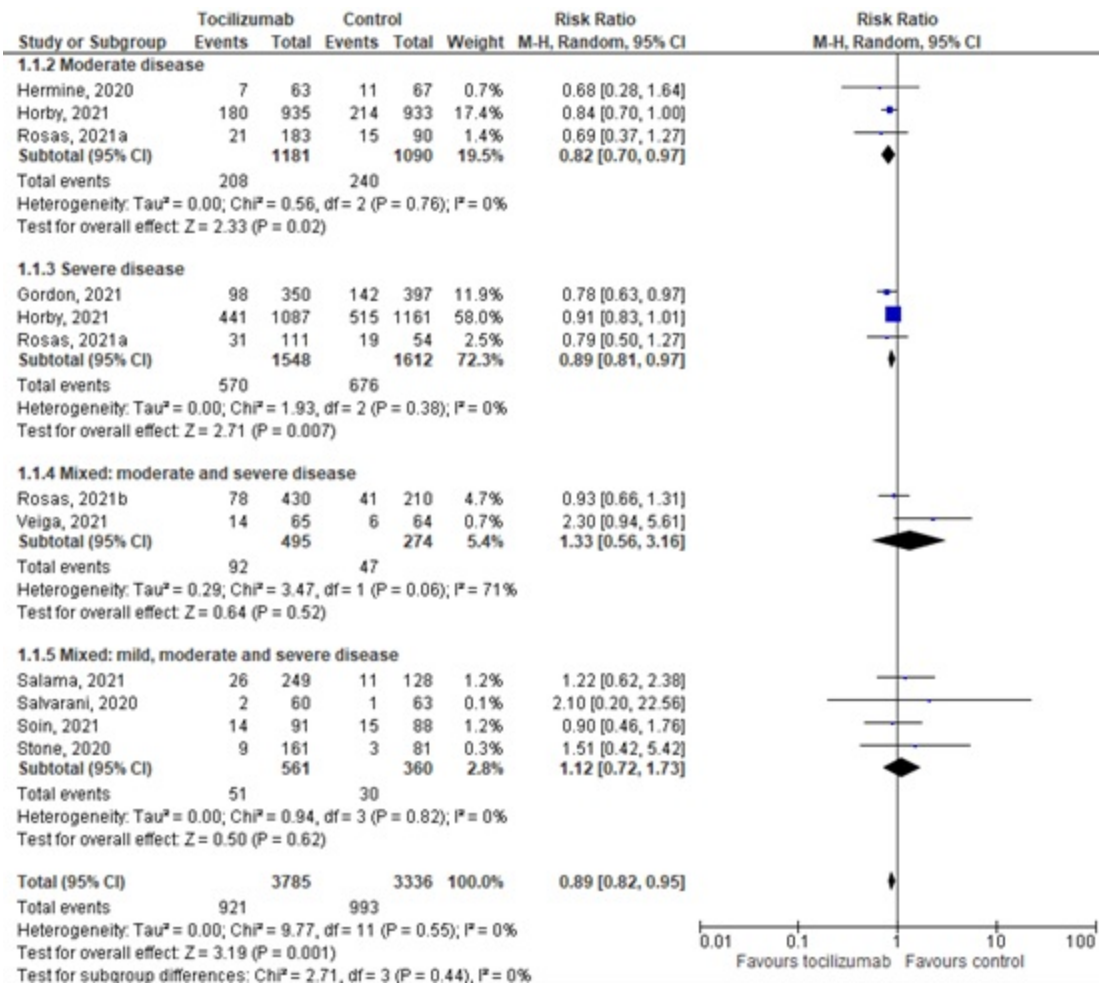
The pooled RR in patients with a moderate or severe disease state was 1.33 (95%CI 0.56 to 3.16), in favour of the control group, for mortality at day 28. The RD was 0.04 (95%CI -0.09 to 0.18). This is considered clinically relevant (*in favour of control*).

Mixed – mild, moderate & severe disease

Four studies reported mortality at day 28 – 30 specifically for patients with a mild, moderate or severe disease state. The pooled RR from these studies was 1.12 (95%CI 0.72 to 1.73) for mortality at day 28. The pooled RD was 0.02 (95%CI -0.02 to 0.05). This is not considered clinically relevant.

There were no studies investigating tocilizumab in patients with mild disease only, and this data could not be extracted from the studies that included a mixed population.

Figure 3. Mortality 21-30 days in hospitalized patients with tocilizumab, per disease severity category



Z: p-value of overall effect; **df:** degrees of freedom; **?**: statistical heterogeneity; **CI:** confidence interval.

Importantly, if sensitivity analyses (i.e., including only the *high quality studies AND studies with more than 80% use of corticosteroids in the standard of care* OR including studies with lower quality and/or initiating less than 80% corticosteroids) were performed for these analyses (i.e., per disease severity category), the same results were shown for (1) moderate disease (Hermine, 2020; Horby, 2021; Rosas2021a), (2) severe disease (Gordon, 2021; Horby, 2021; Rosas, 2021a), and (3) mixed: mild, moderate and severe disease (Salama, 2021; Salvarani, 2021; Soin, 2021; Stone, 2020). Although, except for the disease severity category 'moderate and severe disease'. The RD of the sensitivity for *high quality studies AND studies with more than 80% use of corticosteroids in the standard of care* (Rosas, 2021b) was not considered clinically relevant, but the sensitivity analysis based on lower quality and/or initiating less than 80% corticosteroids was considered clinically relevant (Veiga, 2021).

Level of evidence of the literature

The level of evidence regarding the outcome measure **mortality** started as high, because the studies were RCTs. The level of evidence was downgraded by one level because of inconsistent study results (inconsistency, -1). The level of evidence for the outcome 'mortality' is moderate.

Severe disease

The level of evidence regarding the outcome measure **mortality** started as high, because the studies were RCTs. The level of evidence was downgraded by one level because of imprecision (95% CI crosses threshold of clinical relevance, -1). The level of evidence for the outcome 'mortality' is moderate.

Moderate disease

The level of evidence regarding the outcome measure **mortality** started as high, because the studies were RCTs. The level of evidence was downgraded by one level because of imprecision (95% CI crosses threshold of clinical relevance, -1). The level of evidence for the outcome 'mortality' is moderate.

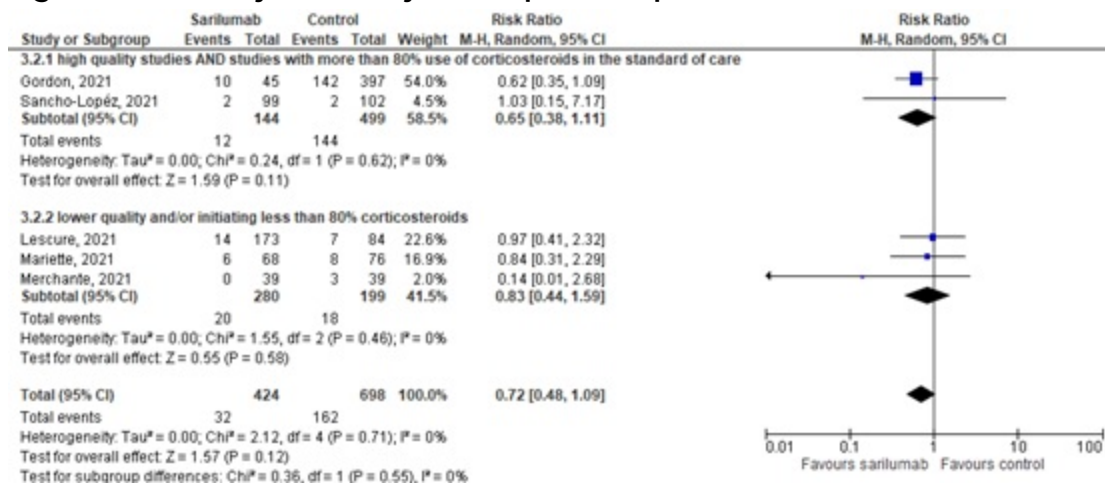
Results – Sarilumab

Mortality at day 21 – 30

Gordon (2021) reported the mortality specifically for patients with a severe disease state at day 21. Merchante (2021), Sancho-López (2021) and Mariette (2021) reported mortality at day 28. Lescure (2021) reported the number of patients alive at day 29. This data was used to calculate mortality at day 29.

The pooled incidence of mortality in hospitalized patients in the intervention group was 32/424 (7.5%), compared to 162/698 (23.2%) in the control group. The pooled relative risk (RR) was 0.72 (95% CI 0.48 to 1.09; Figure 4). The pooled risk difference (RD) was -0.03 (95%CI -0.08 to 0.02), in favour of the intervention group. This is not considered clinically relevant. Regarding the sensitivity analysis (Figure 4), results were in line with the main analysis. The RR in the study with high quality AND the use of more than 80% corticosteroids as part of the standard care was 0.65 (95%CI 0.38 to 1.11), and the RD was -0.06 (95%CI -0.28 to 0.16) (Gordon, 2021; Sancho-López, 2021). This is considered clinically relevant. The pooled RR in studies with lower quality and/or less than 80% corticosteroids was 0.83 (95%CI 0.44 to 1.59), and the RD was -0.0265 (95%CI -0.0756 to 0.0226). This is not considered clinically relevant.

Figure 4. Mortality 21-30 days in hospitalized patients treated with sarilumab 400mg



Z: p-value of overall effect; df: degrees of freedom; ²: statistical heterogeneity; CI: confidence interval.

If possible stratified analyses were performed per disease severity state, see Figure 5.

Moderate disease

Sancho-López (2021) reported the mortality specifically for patients with a moderate disease state. The RR

was 1.03 (95%CI 0.15 to 7.17) and RD was 0.00 (95%CI -0.04 to 0.04). This is not considered clinically relevant.

Mariette (2021) reported the mortality specifically for patients with a moderate disease state. The RR was 0.84 (95%CI 0.31 to 2.29) and RD was -0.02 (95%CI -0.11 to 0.08) at day 28. This is not considered clinically relevant. Mariette (2021) reported the incidence of mortality at day 90 as well. The incidence was 10/68 (15%) in the intervention group, compared with 16/76 (18%) in the control group. This resulted in a RR of 0.70 (95%CI 0.34 to 1.43) and RD of -0.06 (95%CI -0.19 to 0.06). This is considered clinically relevant.

Lescure (2021) reported the mortality specifically for patients with a moderate disease state (i.e., disease was defined by supplemental oxygen administration by nasal cannula, simple face mask, or another similar device). The incidence of mortality in hospitalized patients in the intervention group 400mg was 6/105 (5.7%), compared to 1/55 (1.8%) in the control group. The RR was 3.14 (95%CI 0.39 to 25.5), and RD was 0.04 (95%CI -0.02 to 0.10). This considered clinically relevant (*in favour of the control group*).

Sarilumab 200 mg:

The incidence of mortality in hospitalized patients with a moderate disease state in the intervention group 200mg was 5/92 (5.4%), compared to 1/55 (1.8%) in the control group. This resulted in a RR of 2.99 (95%CI 0.36 to 24.92) and a RD of 0.04 (95%CI -0.02 to 0.09). This considered clinically

The pooled RR in patients with a moderate disease state was 1.07 (95%CI 0.47 to 2.43), and the RD was 0.01 (95%CI -0.02 to 0.04) for mortality at day 28. This is not considered clinically relevant.

Severe disease

Lescure (2021) reported the mortality specifically for patients with a severe disease state (i.e., supplemental oxygen delivered by non-rebreather mask or high-flow nasal cannula, use of invasive or non-invasive ventilation, or treatment in an ICU). The incidence of mortality in hospitalized patients in the intervention group 400mg was 8/68 (11.8%), compared to 6/29 (20.7%) in the control group. This resulted in a RR of 0.57 (95%CI 0.22 to 1.49) and a RD of -0.09 (95%CI -0.26 to 0.08) for mortality at day 29. This is considered clinically relevant.

Sarilumab 200 mg:

The incidence of mortality in hospitalized patients with a moderate disease state in the intervention group 200mg was 10/65 (15.4%), compared to 6/29 (20.7%) in the control group. This resulted in a RR of 0.74 (95%CI 0.30 to 1.85) and a RD of -0.05 (95%CI -0.22 to 0.12). This is considered clinically relevant.

Gordon (2021) reported the mortality specifically for patients with a severe disease state at day 21. The incidence of mortality was 10/45 (22.2%) in patients treated with only additional sarilumab, compared with 142/397 (35.8%) in the control group (i.e., receiving only usual care according to the randomizations). The RR was 0.62 (95%CI 0.35 to 1.09), and RD was -0.14 (95%CI -0.27 to -0.01) for mortality at day 21. This is considered clinically relevant.

The pooled RR in patients with a severe disease state was 0.61 (95%CI 0.37 to 0.99), and the RD was -0.12 (95%CI -0.22 to -0.02) for mortality day 21-30. This is considered clinically relevant.

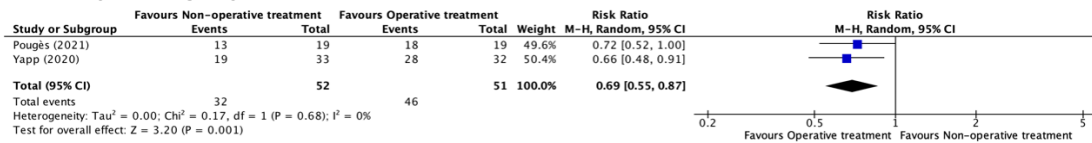
Mild, moderate and severe disease

Merchante (2021) reported the mortality for patients with a mild, moderate or severe disease state. The RR was 0.14 (95%CI 0.01 to 2.68), and RD was -0.08 (95%CI -0.17 to 0.02) for mortality at day 28. This is considered clinically relevant.

Sarilumab 200 mg:

The incidence of mortality in hospitalized patients in the intervention group 200mg was 4/37 (10.1%), compared to 3/39 (7.7%) in the control group. The RR was 1.41 (95%CI 0.34 to 5.86), and RD was 0.03 (95%CI -0.10 to 0.16) was. This is considered clinically relevant (*in favour of the control group*).

Figure 5: Mortality 21-30 days in hospitalized patients treated with sarilumab 400mg, per disease severity category



Z: p-value of overall effect; **df:** degrees of freedom; **τ²:** statistical heterogeneity; **CI:** confidence interval.

Importantly, if sensitivity analyses (i.e., including only the *high quality studies AND studies with more than 80% use of corticosteroids in the standard of care* OR including studies with lower quality and/or initiating less than 80% corticosteroids) were performed for these analyses (i.e., per disease severity category), the same results were shown for (1) moderate disease (Lescure, 2021; Mariette, 2021; *Sancho-Lopéz, 2021*), (2) severe disease (Gordon, 2021; Lescure, 2021) and (3) mixed: mild, moderate and severe disease (Merchante, 2021).

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels because of imprecision (95%CI of the mean difference includes no effect (RD=0) and crosses both thresholds of clinical relevance, -2). The level of evidence for the outcome '*mortality*' is low.

Moderate disease

The level of evidence regarding the outcome measure **mortality** started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of inconsistency (-1), and imprecision (95% CI crosses threshold of clinical relevance, -1). The level of evidence for the outcome '*mortality*' is low.

Severe disease

The level of evidence regarding the outcome measure **mortality** started as high, because the studies were RCTs. The level of evidence was downgraded by one level because of imprecision (95% CI crosses the thresholds of clinical relevance, -1). The level of evidence for the outcome '*mortality*' is moderate.

Results - Levilimab

Lomakin (2021) did not report data about mortality. The initial primary endpoint was overall mortality, but because the mortality was significantly lower than assumed, the study did not have enough power to detect a meaningful difference.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence regarding the

outcome measures **mortality** could not be assessed with GRADE. The outcome measures were not studied in the included studies.

Results - Siltuximab

Declercq (2021) reported mortality during the study (i.e., follow-up of 10-20 weeks), and the estimated mortality at day 28 based on Kaplan-Meier

Mortality, 10-20 weeks

Declercq (2021) reported the number of deaths in the subgroups at follow-up (i.e., 10-20 weeks). The incidence of mortality was 15/75 (20.0 %) in patients treated with only additional siltuximab, compared with 9/74 (12.2%) in the control group (i.e., receiving only usual care according to the randomizations). This resulted in a RR of 1.64 (95%CI 0.77 to 3.52) and a RD of 0.08 (95%CI -0.04 to 0.20). This is considered clinically relevant (*in favour of the control group*).

The incidence of mortality was 5/32 (15.6%) in patients treated with anakinra + tocilizumab, 6/36 (16.7%) in patients treated with anakinra + siltuximab, 10/81 (12.3%) in patients treated with usual care + tocilizumab, and 10/44 (23%) in patients treated with usual care + anakinra. In addition, the estimated mortality at day 28 (i.e., based on Kaplan-Meier) resulted in 13% (95%CI 7 to 23) in the intervention group, compared with 10% (95%CI 5 to 20) in the control group.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of indirectness (other follow-up, -1), and imprecision (95%CI of the mean difference includes no effect (RD=0), crosses both thresholds of clinical relevance, not meeting the optimal information size, -2). The level of evidence for the outcome '*mortality*' is *very low*.

Extensive respiratory support (crucial)

Results - Tocilizumab

Nine studies reported on the outcome extensive respiratory support. All studies reported on the outcome mechanical ventilation. Two of these studies also reported on the outcome non-invasive ventilation and high-flow oxygen combined (Hermine, 2020; Veiga, 2021). One study reported outcomes for patients with a *moderate* disease state only (Hermine, 2021), and one study reported outcomes for patients up to day 21 (Gordon, 2021), respectively.

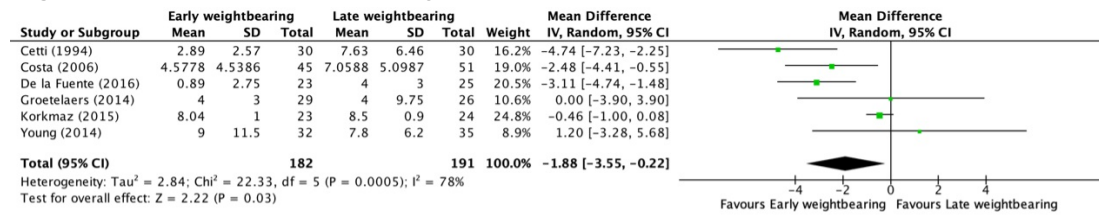
The pooled incidence was 476/2868 (16.6%) in the intervention group compared to 568/2654 (21.4%) in the control group. The pooled RR from these nine studies was 0.79 (95% CI 0.71 to 0.88, Figure 6), in favour of the tocilizumab group. The pooled RD was -0.04 (95% CI -0.06 to -0.02). This is not considered clinically relevant.

Regarding the sensitivity analyses (i.e., high quality study AND >80% corticosteroids as part of the standard care versus low quality study and/or <80% corticosteroids), results were in line with the main analysis (Figure 6). The pooled RR in the high quality studies AND initiating more than 80% corticosteroids was 0.80 (95%CI

0.71 to 0.90), and the RD was -0.04 (95%CI -0.07 to -0.02). This is not considered clinically relevant. The pooled RR in studies with lower quality and/or initiating less than 80% corticosteroids was 0.74 (95%CI 0.59 to 0.93), and the RD was -0.04 (95%CI -0.07 to 0.00). This is not considered clinically relevant.

Salama (2021) reported results for mechanical ventilation or death by day 28, but no results were reported for the effect on mechanical ventilation alone. After excluding this study from the analyses, the pooled RR for the remaining eight studies is 0.80 (95% CI 0.71 to 0.89). The pooled RD remained -0.04 (95% CI -0.06 to -0.02). This is not considered clinically relevant.

Figure 6. Extensive respiratory support in hospitalized patients treated with tocilizumab



Z: p-value of overall effect; df: degrees of freedom; τ^2 : statistical heterogeneity; CI: confidence interval.

Hermine (2020) reported on the outcome mechanical ventilation, non-invasive ventilation or high-flow oxygen on day 14, specifically for patients with a *moderate* disease state. In the tocilizumab group, 11/63 (17.5%) patients received extensive respiratory support (8 patients received non-invasive ventilation or high-flow oxygen and 3 patients received mechanical ventilation). In the control group, 21/67 (31.3%) patients received extensive respiratory support (13 patients received non-invasive ventilation or high-flow oxygen and 8 patients received mechanical ventilation). The RR was 0.56 (95%CI 0.29 to 1.06). The RD was -0.14 (95% CI -0.28 to 0.01). This is considered clinically relevant.

Veiga (2021) reported the need for non-invasive ventilation or high-flow oxygen. In both the tocilizumab group and control group, no patient received non-invasive ventilation or high flow nasal cannula. Veiga (2021) also reported on the outcome mechanical ventilation on day 29 specifically for patients with a moderate or severe disease state. The RR was 0.98 (95%CI 0.26 to 3.77). The RD was -0.00 (95% CI -0.08 to 0.08). This is not considered clinically relevant.

Veiga (2021) also reported on the outcomes on day 8 and 15. The RR for mechanical ventilation on day 8 was 0.78 (95%CI 0.48 to 1.28) and the RD was -0.08 (95%CI -0.24 to 0.08). The RR for mechanical ventilation on day 15 was 0.63 (95% CI 0.26 to 1.51) and the RD was -0.06 (95%CI -0.18 to 0.06). The RR for non-invasive ventilation or high-flow oxygen on day 8 was 0.78 (95%CI 0.48 to 1.28) and the RD was -0.08 (95%CI -0.24 to 0.08). The RR for non-invasive ventilation or high-flow oxygen on day 15 was 0.63 (95% CI 0.26 to 1.51) and the RD was -0.06 (95%CI -0.18 to 0.06). The difference is clinically relevant for 8 and 15 days of follow-up, but not for 29 days.

Gordon (2021) reported progression to invasive mechanical ventilation up to day 21. The incidence was 84/242 (34.7 %) in the intervention group, compared with 116/273 (42.5%) in the control group. The RR was 0.82 (95%CI 0.65 to 1.02). The RD was -0.08 (95% CI -0.16 to 0.01). This is considered clinically relevant.

Level of evidence of the literature

The level of evidence for the outcome measure extensive ventilation started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of inconsistency (-1), and imprecision (crossing the threshold of clinical relevance, -1). The level of evidence for the outcome 'mechanical ventilation' is low.

Results - Sarilumab

Initiation of respiratory support in hospitalized patients with COVID-19 was reported in five studies (Gordon, 2021; Lescure, 2021; Mariette, 2021; Merchante, 2021; Sancho-Lopéz, 2021). This was defined as progression to invasive mechanical ventilation or death, and Brescia-COVID score ≥ 3 at day 15 and day 28 in the study of Sancho-Lopéz (2021). Mariette (2021) defined this outcome as dead or needing non-invasive ventilation or mechanical ventilation on day 14 (i.e., WHO-CPS score > 5). This outcome measure was defined as initiation of mechanical ventilation, non-invasive ventilation, or use of high-flow nasal cannula in the study of Lescure (2021). In the study of Gordon (2021) this outcome measure was defined as progression to invasive mechanical ventilation up to day 21. Merchante (2021) defined this outcome measure as progression to high-flow nasal oxygenation or (non-)invasive mechanical ventilation.

Sancho-Lopéz (2021) reported progression to invasive mechanical ventilation or death in 4/99 (4%) patients in the intervention group, compared with 9/102 (9%) in the control group. This resulted in a RR of 0.46 (95% 0.15 to 1.48) and a RD of -0.05 (95%CI -0.12 to 0.02). This is considered clinically relevant. In addition, the number of patients with a Brescia-COVID score ≥ 3 (i.e., the need of high frequency nasal ventilation, CPAP or non-invasive ventilation or mechanical ventilation) at day 15 and 28 was reported in 16/99 (16%) patients in the intervention group, compared with 16/102 (16%) in the control group. This resulted in a RR of 1.03 (95%CI 0.48 to 2.20) and RD of 0.00 (95%CI -0.10 to 0.11). This is not considered clinically relevant.

Mariette (2021) reported needing non-invasive ventilation or mechanical ventilation or dead at day 14. This incidence was 18/68 (18%) in the intervention group, compared with 20/76 (26%) in the control group. This resulted in a RR of 0.89 (95%CI 0.51 to 1.58) and a RD of -0.03 (95%CI -0.17 to 0.11). By excluding the number of patients who died during the first 14 days, the incidence was 12/68 (18%) in the intervention group, compared with 12/76 (16%) in the control group. This resulted in a RR of 1.12 (95%CI 0.54 to 2.32) and a RD of -0.02 (-0.10 to 0.14). This is not considered clinically relevant.

Gordon (2021) reported progression of initiation of respiratory support in 6/37(16%) patients with *severe* COVID-19 in the intervention group, compared with 116/272 (43%) in the control group. This resulted in a RR of 0.38 (95% CI 0.22 to 2.26) and a RD of -0.26 (95% CI -0.40 to -0.13). This is considered clinically relevant.

Merchante (2021) reported progression to high-flow nasal oxygenation or (non-)invasive mechanical ventilation in 10/39 (25.6%) patients in the intervention group, compared with 5/39 (12.8%) in the control group. This resulted in a RR of 2.00 (95% CI 0.75 to 5.32) and RD of 0.13 (95%CI -0.04 to 0.30). This is considered clinically relevant (*in favour of the control group*).

Sarilumab 200 mg:

Merchante (2021) reported progression to high-flow nasal oxygenation or (non-)invasive mechanical ventilation in 10/37 (27.0%) patients in the intervention group, compared with 5/39 (12.8%) in the control group. This resulted in a RR of 2.11 (95% CI 0.75 to 5.32) and RD of 0.14 (95%CI -0.04 to 0.32). This is

considered clinically relevant (*in favour of the control group*).

Lescure (2021) reported initiation of respiratory support in 33/173(19%) patients in the intervention group, compared with 13/84 (15%) in the control group. This resulted in a RR of 1.23 (95% CI 0.69 to 2.22) and RD of 0.04 (95% CI -0.06 to 0.13). This is not considered clinically relevant.

Sarilumab 200 mg:

Lescure (2021) reported initiation of respiratory support in 26/159 (16%) patients in the intervention group 200mg, compared with 13/84 (15%) in the control group. This resulted in a RR of 1.06 (95% CI 0.57 to 1.95) and a RD of 0.01 (95% CI -0.09 to 0.11). This is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of inconsistency (-1) and imprecision (95%CI of the mean difference includes no effect (RD=0) and crosses both thresholds of clinical relevance, -2). The level of evidence for the outcome '*respiratory support*' is *very low*.

Severe disease

The level of evidence regarding the outcome measure **extensive respiratory support** started as high, because the studies were RCTs. The level of evidence was downgraded by one level of imprecision (not meeting optimal information size, -1). The level of evidence for the outcome '*respiratory support*' is moderate.

Results - Levilimab

Initiation of respiratory support in hospitalized patients with COVID-19 was not reported.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence regarding the outcome measures respiratory support could not be assessed with GRADE. The outcome measures were not studied in the included studies.

Results – other (when results of different IL-6 inhibitors were reported combined, i.e., tocilizumab and siltuximab)

Declercq (2021) defined this outcome as number of invasive ventilation days

Declercq (2021) reported the mean number of invasive ventilator days, which was 5 (95%CI 3 to 7) in the intervention group (i.e., IL-6 blockade group), compared with 5 (95%CI 3 to 9) days in the control group (i.e., no IL-6 blockade group). This resulted in a mean difference of 0 days. This is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of indirectness (1 level, different IL-6 blockades were used as intervention) and imprecision (2 levels, 95%CI of the mean difference includes no effect (RD=0) and crosses both thresholds of clinical relevance). The level of evidence for the outcome '*extensive respiratory support*' is *very low*.

Duration of hospitalization (important)

Results

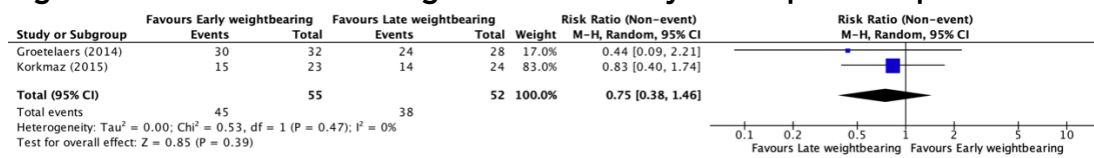
In total, five studies reported the number of patients who were discharged from the hospital after 28-30 days. Results will be displayed per IL-6 inhibitor.

Results - Tocilizumab

Seven studies (Horby, 2021; Rosas, 2021a, Rosas, 2021b; Salama, 2021; Stone, 2020; Veiga, 2021; Wang, 2021) reported time to hospital discharge and three studies (Hermine, 2020, Horby, 2021, Salvarani, 2020) reported the incidence of discharge after a follow-up of 28-30 days. One study reported duration of ICU stay, but not of total hospitalization (Soin, 2021).

Three studies (Hermine, 2020, Horby, 2021, Salvarani, 2020) reported the incidence of discharge after a follow-up of 28-30 days. The pooled incidence of hospital discharge after follow-up was 1256 out of 2145 (58.6%) in the intervention group compared to 1151 out of 2224 (51.8%) in the control group. The pooled RR was 1.08 (95%CI 0.96 to 1.21, Figure 7). The pooled RD was 0.053 (95% CI -0.0004 to 0.1099). This is considered clinically relevant.

Figure 7. Incidence of discharge after 28-30 days in hospitalized patients treated with tocilizumab.



Z: p-value of overall effect; df: degrees of freedom; τ^2 : statistical heterogeneity; CI: confidence interval.

Seven studies (Horby, 2021; Rosas, 2021a, Rosas, 2021b; Salama, 2021; Stone, 2020; Veiga, 2021; Wang, 2021) reported time to hospital discharge. Six of these studies reported the median time to discharge, only Veiga (2021) reported a mean duration. The median time to discharge the studies ranged from 6 to 26 days in the intervention group compared to 6 to >28 days in the control group. In two of the six studies, the difference between intervention and control group was more than 3 days. In the four other studies, the difference between the two groups was 0, 1.5, and 2 days.

One study (Veiga, 2021) reported mean (SD) duration of hospital stay of 11.3 (8.0) days in the tocilizumab group compared to 14.7 (8.2) days in the control group. The mean difference in this study was -3.40 (95%CI -6.20 to -0.60) days. This is considered clinically relevant.

Four studies (Gordon, 2021; Rosas 2021a; Salama, 2021; Stone, 2020) reported the hazard ratio for duration of hospitalization. The HR in the studies ranged from 1.08 (95%CI 0.81 to 1.43) to 1.41 (95%CI 1.18 to 1.70), in favour of the intervention group.

One study (Soin, 2021) reported median time of ICU stay, but not of total hospitalization. The median ICU stay was 7 (IQR 3 to 10) days in the intervention compared to 6 (IQR 3.5 to 11) days in the control group. The difference was 1 day, this is not considered clinically relevant.

Level of evidence of the literature

The level of evidence regarding the outcome measure duration of hospitalization started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels because of inconsistency (different outcomes between studies, -1), and imprecision (crossing the threshold of clinical relevance, -1). The level of evidence for the outcome 'duration of hospitalization' is low.

Results - Sarilumab

Duration of hospitalization in hospitalized patients with COVID-19 was reported in four studies (Lescure, 2021; Mariette, 2021; Merchante, 2021; Sancho-Lopéz, 2021).

Two studies (Mariette, 2021; Merchante, 2021) reported the incidence of discharge after a follow-up of 28-30 days. The pooled incidence of hospital discharge after follow-up was 87 out of 107 (81.3%) in the intervention group compared to 87 out of 115 (75.7%) in the control group. The pooled RR was 1.06 (95%CI 0.94 to 1.20, Figure 8). The pooled RD was 0.052 (95% CI -0.047 to 0.151). This is considered clinically relevant.

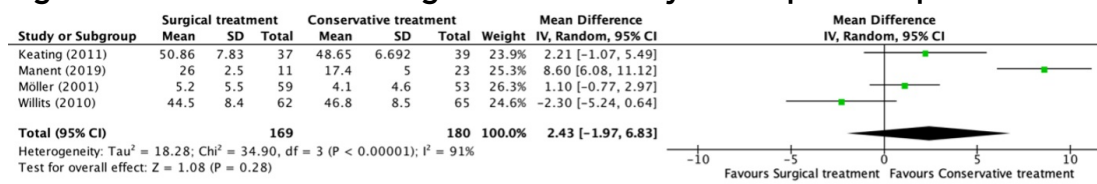
Sarilumab 200 mg:

Merchante (2021) reported that the number of patients which discharged from the hospital within 28 days. A number of 30/37 (81.2%) patients in the intervention group discharged, compared with 34/39 (87.2%) in the control group. This resulted in a RR of 0.93 (95%CI 0.76 to 1.13) and a RD of -0.06 (95%CI -0.23 to 0.10). This difference not clinically relevant.

Sancho-Lopéz (2021) reported the time to hospital discharge in days. This was 7 (95% CI 6-8) days in the intervention group, compared with 7 (95% CI 6-8) days in the control group. The difference was 0 days, this is not considered as a clinically relevant difference.

In addition, the number of patients with ICU admission at day 15 and day 28 was reported. In total 7/99 (7%) patients in the intervention group were admitted to ICU, compared with 10/102 (10%) in the control group, both at day 15 and 28. This resulted in a RR of 0.72 (95% CI 0.29 to 1.82) and a RD of -0.03 (95% CI -0.10 to 0.05). This difference is not clinically relevant.

Figure 8. Incidence of discharge after 28-30 days in hospitalized patients treated with sarilumab.



Z: p-value of overall effect; df: degrees of freedom; τ^2 : statistical heterogeneity; CI: confidence interval.

Lescure (2021) reported that the mean (SE) number of days hospitalization among patients alive at day 60 was 16 days (0.9) in the intervention group (n=173), compared with 16 days (1.3) in the control group (n=84). The difference was 0 days, this is not considered as a clinically relevant difference.

Sarilumab 200 mg:

Lescure (2021) reported that the mean (SE) number of days hospitalization among patients alive at day 60 was 16 days (1.0) in the intervention group 200mg (n=159), compared with 16 days (1.3) in the control group (n=84). The difference was 0 days, this is not considered as a clinically relevant

difference.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels because of inconsistency (different outcomes between studies, -1), and imprecision (95%CI of the mean difference includes no effect (RD/MD=0), -1). The level of evidence for the outcome '*duration of hospitalization*' is *low*.

Results - Levilimab

Duration of hospitalization in hospitalized patients with COVID-19 was reported in one study (Lomakin, 2021). Lomakin (2021) reported the mean (IQR) duration of hospital stay in days. In addition, the number of patients which were transferred to ICU were reported.

Lomakin (2021) reported that the median (IQR) duration was 11 (8-16) days in the intervention group, compared with 11 (7-18) days in the control group. The difference was 0 days. This is not considered as clinically relevant.

In the intervention group 3/103 (3%) were transferred to ICU, compared with 10/103 (10%) in the control group. This resulted in a RR of 0.30 (95%CI 0.09 to 1.06) and a RD of -0.07 (-0.13 to -0.00). This is considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels because of imprecision (95%CI of the mean difference includes no effect (RD=0), and not meeting the optimal information size, -2). The level of evidence for the outcome '*duration of hospitalization*' is *low*.

Results – other (when results of different IL-6 inhibitors were reported combined, i.e. tocilizumab and siltuximab)

Declercq (2021) defined this outcome as median number of days in the hospital and ICU, respectively.

Declercq (2021) reported that the mean number of days in hospital was 20 (95%CI 18 to 22) in the intervention group (i.e., IL-6 blockade group), compared with 19 (95%CI 16 to 22) days in the control group (i.e., no IL-6 blockade group). This resulted in a mean difference of 1 days, which is not considered clinically relevant.

Regarding the number of days at ICU, this was 11 (95%CI 8 to 14) in the intervention group, compared with 10 (95%CI 7 to 15) in the control group. This resulted in a mean difference of -1 day, which is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of indirectness (different IL-6 blockades were used as intervention. -1) and imprecision (95%CI of the mean difference includes no effect (RD=0) and crosses both thresholds of clinical relevance, -2). The level of evidence for the outcome '*duration of hospitalization*' is *very low*.

Time to clinical improvement (important)

Results - Tocilizumab

Four studies (Salama, 2021; Soin, 2021; Stone, 2020; Wang, 2021) reported on the outcome clinical improvement. Three of these studies (Salama, 2021; Soin, 2021; Stone, 2020) reported median time to improvement. Median time to improvement in the studies ranged from 6 to 7 days in the intervention group compared to 5 to 7 days in the control group. The difference of 1 day is not considered clinically relevant. One study (Wang, 2021) reported the cure rate. In the intervention group, 32/34 (94.1%) were cured compared to 27/31 (87.1%) in the control group. The RR was 1.08 (95% CI 0.92 to 1.27). The RD was 0.07 (95%CI -0.07 to 0.21). This is considered clinically relevant.

Level of evidence of the literature

The level of evidence regarding the outcome measure time to clinical improvement started as high, because the studies were RCTs. The level of evidence was downgraded by two levels because of inconsistency (heterogeneity in reporting 'time to clinical improvement', -1) and imprecision (crossing the threshold of clinical relevance, -1). The level of evidence for the outcome 'time to clinical improvement' is low.

Results - Sarilumab

Time to clinical improvement for hospitalized patients with COVID-19 was reported in one study (Lescure, 2021).

Lescure (2021) reported that the median time (95% CI) to NEWS2 of 2 or lower for 24 hours was 9 days (8 to 11) in the intervention group (n=173), compared to 11 days (8 to 14) in the control group (n=84). The difference is 2 days, this is not considered clinically relevant. The median time (95%) to resolution of fever was also reported, which was 9 (7 to 10) in the intervention group (n=173), compared with 7 (6 to 12) in the control group (n=84). The difference is 2 days, this is not considered clinically relevant.

Sarilumab 200 mg:

Lescure (2021) reported that the median time (95% CI) to NEWS2 of 2 or lower for 24 hours was 8 days (7 to 9) in the intervention group 200mg (n=159), compared to 11 days (8 to 14) in the control group (n=84). The difference is 3 days, this is considered clinically relevant. The median time (95%) to resolution of fever was also reported, which was 8 (7 to 9) in the intervention group 200mg (n=159), compared with 7 (6 to 12) in the control group (n=84). The difference is 1 days, this is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 1 level because of imprecision (not meeting the optimal information size, -1). The level of evidence for the outcome 'time to clinical improvement' is moderate.

Results -Levilimab

Time to clinical improvement in hospitalized patients with COVID-19 was not reported.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence regarding the outcome measures **time to clinical improvement** could not be assessed with GRADE. The outcome measures were not studied in the included studies.

Results – other (when results of different IL-6 inhibitors were reported combined, i.e. tocilizumab and siltuximab)

Time to clinical improvement in hospitalized patients with COVID-19 was reported in one study (Declercq, 2021).

Declercq (2021) reported the median (95%CI) time to clinical improvement in days. This was 11 (10 to 16) days in the intervention group (i.e., IL-6 blockade group), compared to 12 (11 to 16) days in the control group. This resulted in a HR of 1.00 (95%CI 0.78 to 1.29). The absolute difference of 1 days is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of indirectness (different IL-6 blockades were used as intervention, -1) and imprecision (95%CI of the mean difference includes no effect (RD=0) and crosses both thresholds of clinical relevance, -2). The level of evidence for the outcome '*time to clinical improvement*' is *very low*.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with an interleukin (IL-)6 inhibitor compared to treatment without an interleukin (IL-)6 inhibitor in patients with COVID-19?

PICO

- P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
- I: IL-6 inhibitor + standard care
- C: standard care only / placebo treatment + standard care
- O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

Relevant outcome measures

For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization, and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days difference for duration of hospitalization and time to clinical

improvement, 5% points absolute difference need for respiratory support and ICU admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 20 January 2022. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in indexed journal, comparing treatment with anti-IL-6 or anti-IL-6-R and standard care to standard care alone or treatment anti-IL-6 or anti-IL-6-R and standard care to placebo and standard care in patients with COVID-19.

The systematic literature search resulted in 80255 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials. Eventually, seventeen studies were included.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, seventeen RCTs were included in the analysis of the literature. Two of the seventeen RCTs studied more than one IL-6 inhibitor; one RCT studied tocilizumab and sarilumab, and one RCT studied tocilizumab and siltuximab. Ten studies described tocilizumab, four studies sarilumab, and one study levilumab. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Interleukine-1 remmers

Uitgangsvraag

Wat is de plaats van interleukine (IL-)1 remmers bij de behandeling van patiënten met COVID-19?

Aanbeveling

IL-1 remmers worden niet aanbevolen als standaardbehandeling voor opgenomen patiënten met COVID-19

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder een IL-1 remmer bij patiënten opgenomen in het ziekenhuis met COVID-19. Tot 24 januari 2022 werden er 6 gerandomiseerde gecontroleerde studies (RCT's) gevonden. Vier studies onderzochten de IL-1 receptor antagonist anakinra (Mariette, 2021; Kyriazopoulou, 2021; Kharazmi, 2021; Declercq, 2021), twee studies bekeken het anti-IL-1-antilichaam canakinumab (Caricchio, 2021; Cremer, 2021). In totaal werden er 1579 patiënten gerandomiseerd (n=847 in de interventiegroep en n=732 in de controlegroep).

Er werden alleen RCT's geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Er waren meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision), waardoor de kwaliteit van dit bewijs naar beneden werd bijgesteld. Daarnaast werden er verschillende uitkomstmaten (heterogenicity) gebruikt bij bijvoorbeeld rapportage van de mortaliteit (14 dagen en 28-30 dagen), waardoor de kwaliteit van dit bewijs waar nodig ook naar beneden werd bijgesteld. De geïnccludeerde patiënten verschilden per studie: Mariette (2021) includeerde patiënten met o.a. een CRP boven de 25, terwijl Kyriazopoulou (2021) een verhoogde (≥ 6 ng ml^{-1}) soluble urokinase plasminogen activator receptor (suPAR) gebruikte. Voor deze verschillen in inclusie werd niet afgewaardeerd in de gradering van de studies, maar zij moeten wel worden meegenomen in de overwegingen.

IL-1 remmers bij patiënten die waren opgenomen in het ziekenhuis

Op basis van de gevonden resultaten kan er met lage zekerheid worden geconcludeerd dat er geen (grote) reductie in de mortaliteit optreedt bij het gebruik van IL-1 remmers (risicoverschil: -2,9%, 95% CI -5,8 tot 0.1; relatief risico: 0.69, 95% CI 0.46 tot 1.03). Deze conclusie komt overeen met de conclusie uit een Cochrane review uit 2022 (Davidson, 2022).

De zes geïnccludeerde gerandomiseerde onderzoeken laten tegenstrijdige resultaten zien: 5 RCT's tonen geen overtuigend voordeel van IL-1 remming, terwijl de studie van Kyriazopoulou (2021) dit wel laat zien.

- Een open-label RCT uit Frankrijk (Mariette, 2021) werd na inclusie van 116 patiënten met mild tot matig ernstige ziekte en PCR-bevestigde SARS-CoV-2 infectie, waarvan 59 in de anakinra groep, voortijdig gestopt omdat uit een tussenanalyse bleek dat geen positief klinisch effect aantoonbaar was (ITT basis). Geïnccludeerd werden patiënten die ten minste 3 L/min O_2 via een masker of neuscanule nodig hadden, maar geen mechanische beatmings, en CRP van meer dan 25 mg/L. Vergeleken werd standaardzorg met of zonder anakinra. De twee primaire uitkomsten waren overlijden op dag 4 of noodzaak tot niet-

invasieve of mechanische beademing en overleven zonder behoefte aan mechanische of niet-invasieve beademing (inclusief high flux zuurstof) op dag 14. Gebruik van anakinra leidde hier niet tot betere klinische resultaten.

- Een Belgische multicenter RCT (Declercq, 2021) randomiseerde 342 opgenomen patiënten met een hoge zuurstofbehoefte of mechanische ventilatie tweemaal: naar anakinra naast SoC versus SoC, en naar IL-6 blokkade (tocilizumab of siltuximab) naast SoC versus SoC. Door deze dubbele randomisatie ontstonden er relatief kleine groepen patiënten in elk stratum. Er werd geen verschil gezien in de tijd tot klinisch herstel en ook geen verschil in de mortaliteit na 28 dagen.
- Een relatief grote RCT bij 594 patiënten met een ernstige COVID-19 infectie, maar geen noodzaak tot (non-)invasieve beademing, toonde wel een positief resultaat van anakinra (Kyriazopoulou, 2021). In deze trial, genaamd SAVE MORE, werden patiënten geïncludeerd nadat zij gemiddeld 9 dagen klachten hadden en een verhoogd serum suPAR (soluble urokinase plasminogen activator receptor; SuPAR ≥ 6 ng/ml). Na 28 dagen bleek de kans op een slecht beloop kleiner in de anakinra-groep, gemeten op een 11-punts-schaal (OR 0.36; 95% CI 0.26-0.50) en ook de mortaliteit na 28 dagen was lager (3.2 vs 6.9%).
- Een relatief kleine Iraanse studie met 30 patiënten toonde een (niet statistisch significant) voordeel van anakinra: de 14 dagen mortaliteit was 33% in de anakinra groep vergeleken met 47% in de controlegroep (Kharazmi, 2021).
- Een gerandomiseerde, placebogecontroleerde fase 3 studie naar een anti-IL-1 beta antistof, canakinumab, includeerde 454 opgenomen patiënten met hypoxie (maar zonder invasieve beademing) en tekenen van systemische hyperinflammatie (Caricchio, 2021). De hyperinflammatie werd gedefinieerd als een CRP van 20 mg/L of meer, of een ferritine van 600 ug/L of meer. De geïncludeerde patiënten kregen een eenmalige gift canakinumab (450 tot 750 mg, afhankelijk van het gewicht) of placebo. Er werd geen verschil gezien in de primaire uitkomstmaat, aangezien 88.8% in de canakinumab-groep en 85.7% in de placebo-groep de eerste 29 dagen overleefden zonder mechanische ventilatie (OR 1.39; CI 95% 0.76-2.54). Ook de COVID-19 gerelateerde mortaliteit was niet statistisch significant verschillend (4.9% in de canakinumab-groep versus 7.2% in de placebo-groep), al werd er wel een numeriek voordeel gezien.
- Een relatief kleine Amerikaanse RCT randomiseerde 45 patiënten met COVID-19 en myocardschade naar twee doseringen canakinumab (300 mg of 600 mg) of placebo (Cremer, 2021). Er werd geen voordeel gevonden voor behandeling met canakinumab op de 28 dagen mortaliteit (60% vs 58% vs 58% respectievelijk).

Concluderend laat slechts 1 RCT een statistisch significant positief effect op mortaliteit en snelheid van klinisch herstel zien met IL-1 remming (Kyriazopoulou, 2021). In dit onderzoek werd anakinra toegediend op geleide van suPAR, een biomarker die op het moment van de samenstelling van deze richtlijn niet standaard in de Nederlandse ziekenhuizen beschikbaar is. De verhouding van de suPAR tot het CRP is op dit moment nog onvoldoende duidelijk, waardoor er (nog) geen alternatieve afkapwaarde van het CRP gedefinieerd kan worden. Ook is het nog onduidelijk waarom er in deze ene studie van Kyriazopoulou een voordeel gezien wordt van IL-1 remming, terwijl de andere studies dit niet laten zien.

Een mogelijke verklaring is het verschil in het gebruik van corticosteroïden in de standaardbehandeling. In de studie van Kyriazopoulou (2021) bevatte de standaardbehandeling in 87% corticosteroïden, hetgeen meer

overeenkomt met de huidige standaardbehandeling, terwijl dit bij Declercq (2021), Cremer (2021) en Kharazmi (2021) tussen de 47% en 63% was. In de studies van Mariette (2021) en Caricchio (2021) kreeg minder dan 40% van de patiënten corticosteroïden toegediend in het kader van de standaardbehandeling.

Andere mogelijke verklaringen voor de gevonden verschillen tussen de studies is de studiepopulatie en de timing van de behandeling met IL-1 remmers. De twee kleinere studies onderzochten een relatief zieke populatie met een mortaliteit in de controlegroep boven de 20% (Mariette, 2021; Kharazmi, 2021). De twee grootste studies hadden een vergelijkbare relatief lage mortaliteit in de controlegroep: ongeveer 7% na 28 dagen bij zowel Carrichio (2021) als Kyriazopoulou (2021). Alhoewel alleen de SAVE MORE studie van Kyriazopoulou een statistisch significant voordeel van IL-1 remming op de COVID-19 gerelateerde mortaliteit liet zien, werd er wel in beide studies een numeriek voordeel gezien van behandeling met IL-1 remming. De inzet van IL-1 remming bij patiënten die minder ernstig ziek zijn, gaat mogelijk gepaard met een groter effect van de behandeling. De suggestie dat IL-1 remming met name ingezet zou kunnen worden in het begin van de inflammatoire fase van COVID-19, werd ook gedaan in een review (Veerdonk, 2021). Daarnaast laat een zevende RCT, die nog niet werd meegenomen in de huidige analyse omdat deze alleen als pre-print beschikbaar was, geen effect zien van anakinra bij patiënten op de intensive care, dus in een late fase van de COVID-19 (Derde, 2021).

Naast de onduidelijkheid over de timing van IL-1 remming, is het onduidelijk of de mogelijke winst van IL-1 remming ook behaald zou worden (of in grotere mate) als de standaardbehandeling ook IL-6 remming bevat, zoals tocilizumab. De studie van Declercq (2021) is te klein om hierover een betrouwbare uitspraak te kunnen doen, maar de beperkte data uit deze studie laten geen aanwijzingen zien voor een additioneel voordeel van IL-1 remming plus IL-6 remming.

Naast de cruciale uitkomstmaat 'mortaliteit', werd er gekeken naar het effect van IL-1 remmers op de noodzaak tot invasieve respiratoire ondersteuning, de duur van hospitalisatie en de tijd tot symptoomresolutie. Met een lage zekerheid werd geconcludeerd dat er een klein tot geen effect zou kunnen optreden op de duur van de ziekenhuisopname. Op basis van de beschikbare literatuur kon er geen betrouwbare uitspraak gedaan worden over het effect van IL-1 remmers op de noodzaak tot invasieve respiratoire ondersteuning of de tijd tot symptoomresolutie hospitalisatie.

Overige overwegingen

Soort IL-1 remmer

In de huidige richtlijn worden de resultaten van de verschillende middelen (anakinra en canakinumab) zo mogelijk gepoold weergegeven. Deze middelen hebben echter niet precies dezelfde werking: anakinra remt zowel IL-1 alfa als IL-1 beta, terwijl canakinumab alleen op IL-1 beta werkt. Ook als de resultaten per middel weer gegeven worden (wat deels in de resultaten is gepresenteerd), verandert de conclusie niet. Op dit moment is het bewijs voor de IL-1 remmer anakinra het sterkst.

Bijwerkingen

Vijf van de geïncludeerde studies rapporteerden het percentage (ernstige) bijwerkingen (Mariette, 2021; Kyriazopoulou, 2021; Kharazmi, 2021; Declercq, 2021; Caricchio, 2021; Cremer, 2021). In geen van de studies werd een significant verschil gevonden. Ook een systematische analyse van Cochrane in patiënten met

COVID-19 concludeerde dat IL-1 remming waarschijnlijk geassocieerd is met geen of nauwelijks toename van het aantal bijwerkingen (Davindson, 2022). Een eerder Cochrane studie naar het gebruik van IL-1 remmers voor andere indicaties zoals reumatoïde artritis, rapporteerde wel iets vaker (ernstige) infecties, maar dit was niet statistisch significant (Mertens, 2009).

Dosering

De dosering anakinra was niet gelijk in de beschreven studies. Kyriazopoulou (2021) en Kharazmi (2021) en Declercq (2021) bestudeerden een dagelijks dosering van 100 mg (injectie) gedurende 7-10 dagen, 14 dagen en 28 dagen, respectievelijk. Mariette (2020) bestudeerde een dosering van 200 mg 2dd op dagen 1-3, 100 mg 2dd op dag 4 en 100 mg 1dd op dag 5. Alleen in de studie van Kyriazopoulou (2021) werd de anakinra subcutaan gegeven, de andere studies gaven het middel intraveneus. De studie van Declercq (2021) randomiseerde de patiënten twee keer. Bij de eerste randomisatie werden patiënten toegewezen aan een behandeling met een IL-1 remmer of een standaardbehandeling, vervolgens werden dezelfde patiënten nogmaals toegewezen aan een (extra) behandeling met een IL-6 remmer of uitsluitend een standaardbehandeling. De twee studies die een eenmalige toediening canakinumab onderzochten, gebruikten ook verschillende doseringen. Caricchio doseerde op basis van gewicht (doseringen tussen de 450 mg en 750 mg) en Cremer randomiseerde naar 300 mg of 600 mg canakinumab. Om deze reden is in alle analyses afgewaardeerd voor inconsistentie.

Virusvarianten

Sinds de opkomst van de omikron variant van SARS-CoV-2 in Nederland eind 2021, is de kans op een ernstig beloop van COVID-19 op populatieniveau zeer sterk gedaald. Het is van belang om op te merken dat de besproken gerandomiseerde studies werden verricht voor de opkomst van de omikron variant. Het is onduidelijk wat de invloed is van deze variant op het effect van anti-inflammatoire therapie, al wordt aangenomen dat patiënten die door de omikron variant een ernstige COVID-19 infectie ontwikkelen nog steeds baat hebben bij anti-inflammatoire therapie. De 'number needed to treat' zou wel anders (vermoedelijk hoger) kunnen zijn.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens worden IL-1 remmers op dit moment niet aanbevolen in de standaardbehandeling van COVID-19. Wel worden deze middelen in verschillende klinische trials onderzocht. De resultaten van deze studies zullen bepalen of er een plek is voor IL-1 remmers in de behandeling van COVID-19 en bij welke patiëntenpopulatie.

Kosten (middelenbeslag)

Gezien het gebrek aan overtuigend bewijs voor effectiviteit wordt IL-1 remming nu niet aanbevolen in de standaardbehandeling van patiënten met COVID-19.

Aanvaardbaarheid, haalbaarheid en implementatie

IL-1 remmers worden niet voorgeschreven in de standaardbehandeling van COVID-19, dus de werkgroep voorziet geen problemen qua implementatie. Wel worden deze middelen in verschillende klinische trials onderzocht. De resultaten van deze studies kunnen in de toekomst de plaatsbepaling van IL-1 remmers voor bepaalde patiëntgroepen veranderen.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Het is nog onvoldoende duidelijk of IL-1 remmers een effectieve behandeling van COVID-19 zijn, in welke fase van het beloop van COVID-19 zij gegeven zouden moeten worden, en op basis van welke beschikbare markers.

Onderbouwing

Achtergrond

Een infectie met SARS-CoV-2 kan leiden tot een ernstige pneumonie en ARDS. Een dysregulatie van de immuunrespons lijkt bij COVID-19 een belangrijke rol in de pathofysiologie te spelen (Veerdonk, 2021). Er zijn verschillende middelen onderzocht met anti-inflammatoire werking, waaronder IL-1 remmers. De IL-1 receptor antagonist (IL-1RA) anakinra, dat zowel IL-1 alfa als IL-1 beta remt, werd al vroeg onderzocht bij patiënten met bacteriële sepsis (Opal, 1997). Alleen in een post-hoc analyse bij de subgroep van patiënten met een bacteriële sepsis en leverfunctiestoornissen en tekenen van diffuse intravasale stolling als uiting van macrofagen activatie syndroom (MAS, 6% van totale groep), werd een gunstig effect op overleving gezien (Shakoory, 2016). In een studie met long-epitheelcellen die geïnfecteerd werden met rat-specifieke Corona-virussen was de chemokine-expressie minder na blootstelling aan anakinra. Een eerste patiëntenserie uit Italië toonde aan dat er mogelijk ook klinische winst te bereiken was ten opzichte van historisch controles (Cavalli, 2020).

Inmiddels is in verschillende gerandomiseerde studies (RCT's) de effectiviteit van IL-1 remmers onderzocht om de plaats van deze middelen bij de behandeling van COVID-19 patiënten te bepalen. Klinische dose-finding studies zijn in deze setting nooit verricht. De groep IL-1 remmers bevat zowel IL-1 receptor antagonisten (IL-1RA; anakinra) als anti-IL-1 beta antistoffen (canakinumab).

Conclusies / Summary of Findings

Mortality (crucial)

Low GRADE	Treatment with an IL-1 inhibitor may result in reduced mortality when compared with treatment without an IL-1 inhibitor in <u>hospitalized</u> patients with COVID-19. <i>Source: Caricchio, 2021; Cremer, 2021; Declercq, 2021; Kharazmi, 2021; Kyriazopoulou, 2021; Mariette, 2021.</i>

Extensive respiratory support (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with an IL-1 inhibitor on the need for extensive respiratory support when compared with treatment without an IL-1 inhibitor in <u>hospitalized</u> patients with COVID-19. <i>Source: Caricchio, 2021; Cremer, 2021; Declercq, 2021; Kharazmi, 2021; Kyriazopoulou, 2021; Mariette, 2021.</i>

Duration of hospitalization (important)

Low GRADE	Treatment with an IL-1 inhibitor may result in little to no difference in length of stay when compared with treatment without an IL-1 inhibitor in <u>hospitalized</u> patients with COVID-19. Source: Caricchio, 2021; Declercq, 2021; Kharazmi, 2021; Kyriazopoulou, 2021; Mariette, 2021.

Time to clinical improvement (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with an IL-1 inhibitor on time to clinical improvement when compared with treatment without an IL-1 inhibitor in <u>hospitalized</u> patients with COVID-19. Source: Cremer, 2021; Declercq, 2021.

Samenvatting literatuur

Anakinra

Declercq (2021) (COV-AID) reported a multicentre (n=16), open label, randomised controlled phase 3 trial in Belgium. They aimed to assess whether tocilizumab, siltuximab or anakinra shortened the time to clinical improvement in patients with COVID-19. Patients were eligible for randomization if they met the inclusion criteria (e.g., PaO₂/FiO₂ < 350 on room temperature or < 280 on supplemental oxygen and bilateral pulmonary infiltrates; use invasive mechanical ventilation, OR non-invasive ventilation or continuous use of CPAP for hypoxia, OR oxygen supplementation with an oxygen flow of at least 10 L/min independent of delivery system). In total 342 patients were randomly assigned to treatment with anakinra and standard care (n=112) or only standard care (n=230), and simultaneously randomly assigned to IL-6 blockade (n=227; 114 for tocilizumab and n=113 for siltuximab) or no IL-6 blockade (n=115). Therefore, 44 patients received only anakinra, 32 patients received anakinra + tocilizumab, 36 patients received anakinra + siltuximab, 81 patients received only tocilizumab, 75 patients received only siltuximab, and 74 patients received only standard care. Most patients received hydroxychloroquine (i.e., 42% assigned before August 2020) or dexamethasone (i.e., 84% assigned from August 2020) as standard care. In total, 60% used corticosteroids as part of the standard care. The median (IQR) age was 67 (56-74) years in the intervention group (i.e., IL-1 blockade group), compared with 64 (54-72) in the control group (i.e., no IL-1 blockade group). In the intervention group 87/112 (77.7%) were males, compared with 178/230 (77.3%) in the control group. The length of the follow-up was 28 days. The following relevant outcome measures were included; duration of hospitalization, time to clinical improvement, respiratory support. The primary outcome was time to clinical improvement. This resulted in a median (range) of 12 days (10-16) in the intervention group, compared with 12 days (10-15) in the control group, HR: 0.94 (95%CI 0.73 to 1.21). There are some concerns regarding risk of bias as the study had an open label design.

Kharazmi (2021) described an open label, randomized controlled trial performed in Iran. Kharazmi (2021) assessed the efficacy and safety of anakinra in patients hospitalised with COVID-19. Patients were eligible for randomization if they met the inclusion criteria (e.g., oxygen saturation less than or equal to 93% measured using a peripheral capillary pulse oximeter; fever (core temperature of 37.8 or more); cough or shortness of breath; PaO₂/FiO₂ less than 300). In total 30 patients were included and randomized to treatment with

anakinra and standard care (i.e., standard protocol for COVID-19, n=15) or only standard care (n=15). Standard medication to treat COVID-19 were corticosteroid (73.3% intervention, 53.3% control), interferon (93.3% intervention, 60.0% control), lopinavir/ritonavir (46.7% intervention, 80.0% control), remdesivir (13.3% intervention, 26.7% control), favipiravir (60.0% intervention, 26.7% control). The mean age ($\pm$ SD) was 49 ($\pm$ 19) years in the intervention group, compared with 59 ($\pm$ 2) years in the control group. In the intervention group 8/15 (53.3%) patients were males, compared with 11/15 (73%) in the control group. The length of the follow-up was 14 days. The following relevant outcome measures were included; duration of hospitalization. The primary outcome was need for endotracheal intubation. This was reported in 3/15 (20.0%) patients in the intervention group, compared with 10/15 (66.7%) in the control group. The rate difference was 46.7%. There are some concerns regarding risk of bias due to the relative short follow-up of 14 days, the open label design (without placebo), and the fact that the study was a pilot study with a small sample size.

Kyriazopoulou (2021) (SAVE-MORE) described a phase 3, double-blind placebo-controlled, multicenter randomized controlled trial. Kyriazopoulou (2021) evaluated anakinra in addition to standard of care versus standard of care alone in patients admitted to the hospital with COVID-19. Dexamethasone was mostly used as standard care (i.e., 86%). In total 594 patients were included as they met the inclusion criteria (e.g., findings in chest X-ray or chest computed tomography compatible with lower respiratory tract infection; need for hospitalization; plasma suPAR [soluble urokinase-type plasminogen activator receptor] $\geq$ 6 ng/ml). At baseline 544/594 (92%) patients needed oxygen administration, 50/594 (8.4%) was diagnosed with a moderate pneumonia (based on WHO classification for COVID-19), and 544/594 (91.6%) with a severe pneumonia. Importantly, patients which needed non-invasive ventilation (NIV) (CPAP or BPAP) or mechanical ventilation were excluded according to the exclusion criteria.

The mean ($\pm$ SD) age was 62 ($\pm$ 12) years, and 344/594 (57.9%) of them were males. Patients in the intervention group (n=405) received anakinra daily for 7 to 10 days (injection, 100 mg of anakinra at a final volume of 0.67ml). The control group (n=189) received placebo (i.e., daily injection of 0.67 ml of 0.9% sodium chloride). The length of the follow-up was 28 days. The following relevant outcome measures were included; mortality, duration of hospitalization (i.e., number of days of hospitalization, time of ICU stay), need for respiratory support. The primary outcome was overall comparison of the distribution of frequencies of the scores from the 11-point WHO-CPS between the two arms of treatment on day 28. This resulted in a odds ratio of 0.36 (95% CI 0.26 to 0.50), in favour of anakinra.

Mariette (2021) (CORIMUNO-ANA-1) described the results of an open-label, Bayesian randomised clinical trial nested within the CORIMUNO-19 cohort. Patients with mild to moderate COVID-19 pneumonia, severe acute respiratory syndrome were selected from 16 hospitals in France. Eligible patients (i.e., C-reactive protein serum concentration > 25 mg/L not requiring admission to ICU at time of admission; mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving at least 3 L/min of oxygen but without ventilation assistance (eg, high-flow oxygen, non-invasive ventilation, or mechanical ventilation) were randomized to receive anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5) with standard care or only standard care (i.e., at the discretion of the site clinicians). At baseline patients were mostly treated with anticoagulants (59% intervention, 53% control), Azithromycin (19% intervention, 25% control) or glucocorticoids (12% intervention, 15% control). In total 116 patients were included, but two of them withdrew consent. Therefore 59/114 (51.7%) were randomized to the intervention group, and 55/114 (48.2%) to the control group. The median age (IQR) was 67 (55.5 to 74) and 65 (59.5 to 78) in the intervention

and control group, respectively. The length of the follow-up was 90 days. The following relevant outcome measures were included; mortality (i.e., at day 28), duration of hospitalization, respiratory support. The study reported two primary outcomes; proportion of patients who had died or needed non-invasive or mechanical ventilation by day 4 (i.e., 21/59 (35.6%) patients in the intervention group vs. 21/55 (38.2%) controls (difference -2.5% (95%CI -17.1 to 12.0)), and survival with no need for mechanical or non-invasive ventilation at day 14 (i.e., 28/59 (47%) patients in the intervention group vs. 28/55 (51%) controls (RR 0.97 (95%CI 0.62 to 1.52)). Importantly the current study was stopped early as no (positive) clinical effect was shown at the interim analysis.

Canakinumab

Caricchio (2021) (CAN-COVID) described a phase 3, double-blind placebo-controlled, multicenter randomized controlled trial, which was conducted in 39 hospitals in Europe and the US. They evaluated the efficacy and safety of canakinumab in patients hospitalized with severe COVID-19. In total 454 patients were included as they met the severity criteria (e.g., had hypoxemia but did not require invasive mechanical ventilation (IMV); diagnosis of infection with SARS-CoV-2 within 7 days prior to randomization; diagnosis of pneumonia with pulmonary infiltrates on chest x-ray or computed tomographic scan within 5 days prior to randomization; peripheral capillary oxygen saturation of 93% or less on room air or arterial oxygen partial pressure/fraction of inspired oxygen less than 300). These patients were randomized to receive canakinumab or placebo. In total 227 patients were included in the intervention group, but 2 withdrew consent. Also 227 patients were included in the placebo group, but 4 patients did not receive placebo. The median (IQR) age was 59 (49-69) years in the intervention group, compared with 57 (50-68) years in the placebo group. In the intervention group 135/227 (59.4%) were males, compared with 132/227 (58.1%) in the control group. Patients in the intervention group received a single dose of canakinumab (450 mg for body weight of 40-<60 kg, 600 mg for 60-80 kg, and 750 mg for >80 kg, see Table 1), and patients in the control group received placebo. In addition, all patients continued to receive standard care treatment for COVID-19 per local practice. Medication which was initiated prior to day 1 was heparin (any dose, 73% both groups), dexamethasone (≥ 6 mg/d; 41% intervention, 32% placebo), azithromycin (37% both groups), remdesivir (22% intervention, 20% placebo), hydroxychloroquine (14% intervention, 13% control), and convalescent plasma or serum (3.5% in both groups). The length of the follow-up was 127 days, but an interim analysis is reported with a follow-up of 29 days in the current publication. The following relevant outcome measures were included; mortality, duration of hospitalization, respiratory support. The primary outcome was survival without IMV from day 3 to day 29. This was achieved in 198/223 (88.8%) patients in the intervention group, compared with 191/223 (85.6%) patients in the placebo group. This resulted in a difference of 3.1 % (95%CI -3.1 to 9.3).

Cremer (2021) (Three C study) described a double-blind, multicenter randomized controlled trial, which was conducted in 5 hospitals in Cleveland (the US). They evaluated the efficacy and safety of canakinumab in patients hospitalized with COVID-19. In total 45 patients were included as they met the inclusion criteria (e.g., hospitalized due to COVID-19 infection, documented SARS-CoV2 acute myocardial injury: Defined as upper respiratory tract specimen positive for COVID-19 and troponin greater than 99th percentile upper reference range without signs or symptoms of acute myocardial ischemia, NT-proBNP or BNP (brain natriuretic peptide) higher than upper reference limit, receiving current standard therapy, C-reactive protein (CRP) > 50 mg/L). These patients were randomized to receive canakinumab (600 mg [i.e., I1] or 300 mg [i.e., I2]) or placebo. Fifteen patients were included in the I1, 14 patients in I2, and 16 patients in the placebo group. The median

(IQR) age was 68.8 (56.1-74.3) years, and 33/45 (73.3%) were males. Patients in the intervention group received a single dose of canakinumab (see Table 1), and patients in the placebo group received placebo. In addition, all patients continued to receive standard care treatment for COVID-19 per local practice. Medication which was initiated was antibiotics related to non-COVID-19 infections, antivirals related to COVID-19, corticosteroids, use of convalescent plasma, and other immunosuppressive agents. The length of the follow-up was 28 days. The following relevant outcome measures were included; mortality, respiratory support, and time to clinical improvement. The primary outcome was time to clinical improvement up to Day 14, defined as the time in days from randomization to either an improvement of two points on seven category ordinal scale or discharge from the hospital, whichever occurred first. This was achieved in 9/15 (60.0%) of the patients in I1, 7/14 (58.1%) patients in I2, and 9/16 (58.3%) in the control group. This resulted in a relative risk of 1.15 (95% CI 0.46 to 2.91) for I1 vs. control, and 0.61 (95% CI 0.23 to 1.64) for I2 vs. control.

Note: The authors published the study design and baseline characteristics of the first 20 patients earlier (Sheng, 2020). In the current summary of literature, the study of Cremer (2021) was used, which reported results of the primary and secondary endpoints of 30 patients.

Table 1. Overview of RCTs comparing IL-1 inhibitors with standard care (or placebo) in hospitalized COVID-19 patients.

Author	Disease severity, based on need for respiratory support*	Sample size	Dosage
Anakinra			
Declercq (2021)	Mixed: The majority of the patients needed administration of oxygen at baseline. <i>Intervention:</i> - no oxygen; N=1 - requiring supplemental oxygen; N=50 - on non-invasive ventilation or high flow oxygen devices; N=44 - on invasive mechanical ventilation; N=17 <i>Control:</i> - no oxygen; N=5 - requiring supplemental oxygen; N=119 - on non-invasive ventilation or high flow oxygen devices; N=84 - on invasive mechanical ventilation; N=22	I: N=112 C: N=230 Total: N=342	Patients allocated to the active drug were daily injected with 100 mg of anakinra in addition to standard care until discharge or a maximum of 28 days. For the second randomization, a subgroup received siltuximab (11 mg/kg i.v. [single injection]) OR tocilizumab (8 mg/kg i.v. [not exceeding 800 mg; single injection])

Kharazmi (2021)	Mixed: Moderate I; 3/15 (20%) C; 6/15 (40%) Severe: I; 12/15 (80%) C; 9/15 (60%)	I: N=15 C: N=15 Total: N=30	Patients allocated to the active drug were daily injected with 100mg of anakinra in addition to standard care until discharge or a maximum of 14 days.
Kyriazopoulou (2021)	Mixed: The majority of the patients needed administration of oxygen at baseline. Although patients were excluded if ratio or partial oxygen pressure to fraction of inspired oxygen less than 150 mmHg or need for NIV (CPAP or BPAP) or mechanical ventilation.	I: N=405 C: N=189 Total: N=594	Patients allocated to the active drug were daily injected with 100 mg of anakinra for 7 to 10 days.
Mariette (2021)	Moderate: Mild-to-moderate COVID-19 pneumonia with a WHO-CPS score of 5 points, receiving <i>at least 3 L/min of oxygen</i> but without ventilation assistance (e.g., high-flow oxygen, non-invasive ventilation, or mechanical ventilation).	I: 59 C: 55 Total: 114	Patients allocated to the active drug received anakinra (200 mg twice a day on days 1–3, 100 mg twice on day 4, 100 mg once on day 5)
Canakinumab			
Caricchio (2021)	Mixed: The majority of the patients needed administration of oxygen at baseline. Regarding the WHO ordinal SCALE I: <i>Intervention:</i> - no oxygen; N=14 - oxygen by mas or nasal prongs; N=161 - non-invasive ventilation or high-flow oxygen; N=52 <i>Control:</i> - no oxygen; N=12 - oxygen by mas or nasal prongs; N=160 - non-invasive ventilation or high-flow oxygen; N=52	I: N=227 C: N=227 Total: N=454	Patients allocated to the active drug received a single dose of canakinumab (450 mg for body weight of 40- <60 kg, 600 mg for 60-80 kg, and 750 mg for >80 kg)
Cremer (2021)	Mixed: the majority needed supplementary oxygen at baseline: - requiring invasive mechanical ventilation: 22.2% - requiring nasal high-flow oxygen and/or non-invasive ventilation: 24.4% - requiring supplemental oxygen: 44.4% - not requiring oxygen: 8.9%	I1: N=15 I2: N=14 C: N=16 Total: N= 45	Patients allocated to the active drug received a single dose of canakinumab. Intervention group 1 received 600 mg, and intervention group 2 received 300 mg.

*Disease severity categories:

- *mild disease (no supplemental oxygen);*
- *moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);*
- *severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).*

N: Total sample size; I: Intervention; C: Control

Results – IL-1 inhibitors

Since the number of studies and the number of patients included was relatively limited, we report all outcomes for the different IL-1 inhibitors combined. Also conclusions were reported for all IL-1 inhibitors combined.

Caricchio (2021) and Cremer (2021) included patients treated with canakinumab, the other studies treated patients with anakinra. Importantly, Cremer (2021) studied two interventions, namely 600 mg canakinumab or 300 mg canakinumab. Outcomes were only reported separately. Therefore, as 300 mg is a reduced dose, the 600 mg canakinumab was used in the main analysis, and the results for the 300 mg intervention were reported as 'additional analysis'.

Mortality (crucial)

Caricchio (2021), Cremer (2021), Kyriazopoulou (2021) and Mariette (2021) reported mortality at day 28 in hospitalized patients with COVID-19. The results are presented separately for a follow-up of 28-30 days. Declercq (2021) reported mortality during the study (i.e., follow-up of 10-20 weeks), and the estimated mortality at day 28 based on Kaplan-Meier. Kharazmi (2021) reported mortality at day 14. These results are described separately.

Mortality, 28-30 days

Caricchio (2021) reported the mortality for patients with a mild, moderate, or severe disease state. The mortality was 12/227 (5.3%) in the intervention group, compared with 16/227 (7.0%) in the control group. The RR was 0.75 (95%CI 0.36 to 1.55), and RD was -0.02 (95%CI -0.06 to 0.03). This is not considered clinically relevant.

Cremer (2021) reported the mortality for patients with a mild, moderate, or severe disease state. The incidence was 1/15 (6.7%) in the intervention group, compared with 3/16 (19.0%) in the control group. The RR was 0.36 (95%CI 0.04 to 3.05), and RD was -0.12 (95%CI -0.35 to 0.11). This is considered clinically relevant.

Additional analysis 300 mg canakinumab

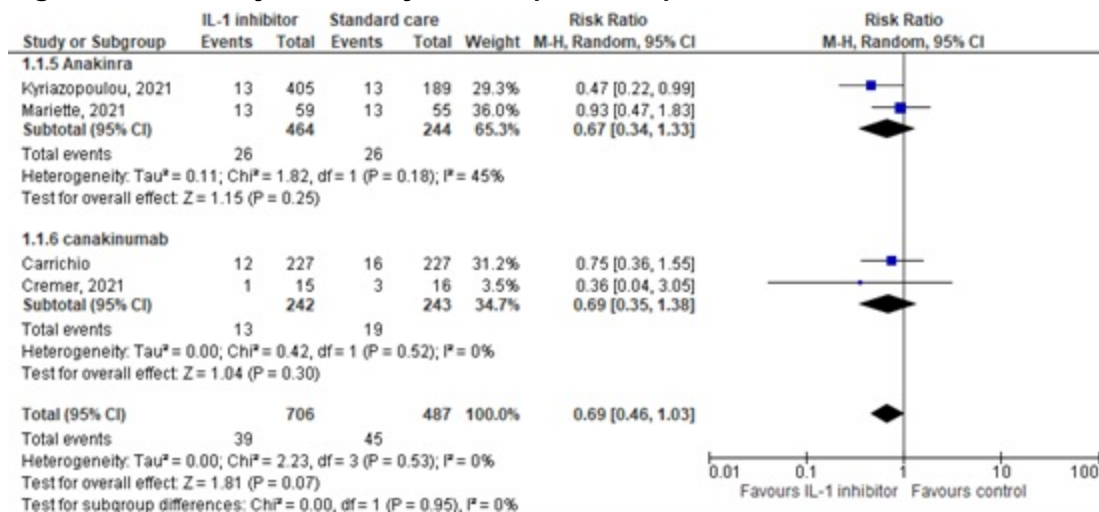
The incidence of mortality was 3/14 (21.4%) in patients treated with canakinumab 300mg, compared with 3/16 (18.8%) in the control group. This resulted in a RR of 1.14 (95% CI 0.27 to 4.78) and a RD of -0.02 (95%CI -0.06 to 0.03).

Kyriazopoulou (2021) reported the mortality specifically for patients with a mild or moderate disease state. The incidence was 13/405 (3.2%) in the intervention group, compared with 13/89 (6.9%) in the control group.

The RR was 0.47 (95%CI 0.22 to 0.99), and RD was -0.04 (95%CI -0.08 to 0.00). This is considered clinically relevant.

Mariette (2021) reported the mortality specifically for patients with a moderate disease state. The incidence was 13/59 (22.0%) in the intervention group, compared with 13/55 (23.6%) in the control group. The RR was 0.93 (95%CI 0.47 to 1.83), and RD was -0.02 (95%CI -0.17 to 0.14). This is not considered clinically relevant.

Figure 1: Mortality (28-30days) in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Mortality, during the study

Declercq (2021) reported the number of deaths in the subgroups at a follow-up of 10-20 weeks. The incidence of mortality was 10/44 (22.7%) in patients treated with only additional anakinra, compared with 9/74 (12.2%) in the control group (i.e., receiving only usual care according to the randomizations). This resulted in a RR of 1.87 (95% CI 0.82 to 4.24) and a RD of 0.11 (95% CI -0.04 to 0.25). This is considered clinically relevant.

The incidence of mortality was 5/32 (15.6%) in patients treated with anakinra + tocilizumab, 6/36 (16.7%) in patients treated with anakinra + siltuximab, 10/81 (12.3%) in patients treated with usual care + tocilizumab, and 15/75 (20.0%) in patients treated with usual care + siltuximab.

In addition, the estimated mortality (i.e., based on Kaplan-Meier) at day 28 resulted in 16% (95% CI 8 to 31) in the intervention group, compared with 10% (95% CI 5 to 20) in the control group. This is considered clinically relevant, in favour of the control group.

Mortality, 14 days

Kharazmi (2021) reported the mortality at day 14 for patients with a moderate, or severe disease state. The incidence of mortality was 5/15 (33.3%) in the intervention group, compared with 7/15 (46.7%) in the control group. The RR was 0.71 (95%CI 0.29 to 1.75), and RD was -0.13 (95%CI -0.48 to 0.21). This is considered clinically relevant.

Note: It was not possible to perform stratified analyses per disease severity category as these results could not be obtained in the publications. Most of the studies included patients with mild, moderate or severe disease state at baseline, see Table 1.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels, because of inconsistency (1 level, due to considerable heterogeneity between the studies regarding medication and/or dose), and imprecision (1 level, 95% CI of the mean difference includes no effect [RD=0]). Therefore, level of evidence for the outcome '*mortality*' is considered *low*.

Extensive respiratory support (crucial)

Initiation of mechanical respiratory support in hospitalized patients with COVID-19 was reported in six studies (Caricchio, 2021; Cremer, 2021; Declercq, 2021; Kharazmi, 2021; Kyriazopoulou, 2021; Mariette, 2021). In the study of Caricchio (2021) this was defined as (1) intubation and mechanical ventilation and (2) ventilation plus additional organ support (vasopressors, kidney replacement therapy [KRT], ECMO). Cremer (2021) defined this outcome as requiring high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation, extracorporeal membrane oxygenation (ECMO or ECLS). Declercq (2021) defined this outcome as number of invasive ventilation days. Kharazmi (2021) defined this as number of patients requiring (1) invasive mechanical ventilation or extracorporeal membrane oxygenation, or (2) non-invasive ventilation or high flow oxygen, at day 7 and 14. This was defined as (1) the need for high-flow oxygen or non-invasive ventilation, (2) initiation of mechanical ventilation with P/F >150 mmHg, (3) initiation of mechanical ventilation with P/F <150 mmHg or vasopressors, (4) initiation of mechanical ventilation with P/F < 150 mmHg and vasopressors or haemodialysis or ECMO in the study of Kyriazopoulou (2021). In the study of Mariette (2021) this outcome was defined as the proportion of patients who had died or needed non-invasive or mechanical ventilation by day 14 (i.e., a score of >5 points on the WHO-CPS) at day 14.

Caricchio (2021) reported initiation of respiratory support in 2 categories. In the intervention group 5/227 (2.2%) needed intubation and mechanical ventilation, compared with 2/227 (0.8%) in the control group. This resulted in a RR of 2.50 (95% CI 0.49 to 12.75) and a RD of 0.01 (95%CI -0.01 to 0.04). This is not considered clinically relevant.

In addition, 2/227 (0.8%) patients in the intervention group needed ventilation plus additional organ support (pressors, KRT, ECMO), compared with 8/227 (3.5%) in the control group. This resulted in a RR of 0.25 (95% CI 0.05 to 1.16) and a RD of -0.03 (95% CI -0.05 to 0.01). This is not considered clinically relevant (<-0.03, due to rounding displayed as -0.03).

Cremer (2021) reported the number of patients requiring invasive respiratory support at day 14 and day 28. At day 14, 5/16 (31.1%) patients in the intervention group required invasive respiratory support, compared with 2/14 (14.3%) in the control group. This resulted in a RR of 2.19 (95%CI 0.50 to 9.56) and a RD of 0.17 (95% CI -0.12 to 0.46). However, two patients in the control group died before day 14. At day 28, 1/15 (6.3%)

patients in the intervention group required invasive respiratory support, compared with 1/13 (7.7%) in the control group. This resulted in a RR of 0.87 (95% CI 0.06 to 12.52) and a RD -0.01 (95%CI -0.20 to 0.18). However, one patient died in the intervention group, and three patients in the control group.

Additional analysis 300 mg canakinumab

At day 14, 1/11 (9.1%) patients in the intervention group required invasive respiratory support, compared with 2/14 (14.3%) in the control group. This resulted in a RR of 0.64 (95% CI 0.07 to 6.14) and a RD of -0.05 (95% CI -0.30 to 0.20). However, three patients died in the intervention group, and two patients in the control group.

At day 28, 1/11 (9.1%) patients in the intervention group required invasive respiratory support, compared with 1/13 (7.7%) in the control group. This resulted in a RR of 1.18 (95% CI 0.08 to 16.78) and a RD 0.01 (95% CI -0.21 to 0.24). Three patients died in the intervention group, and three patients in the control group.

Declercq (2021) reported the mean number of invasive ventilator days, which was 5 (95%CI 3 to 9) in the intervention group (i.e., IL-1 blockade group), compared with 5 (95%CI 3 to 7) days in the control group (i.e., no IL-1 blockade group). This resulted in a mean difference of 0 days. This is not considered clinically relevant.

Kharazmi (2021) reported initiation of respiratory support at 2 different time points.

In the intervention group 2/15 (13.3%) patients were on invasive mechanical ventilation or extracorporeal membrane oxygenation or on non-invasive ventilation or high flow oxygen, compared with 5/15 (33.3%) in the control group at day 7. This resulted in a RR of 0.40 (95% CI 0.092 to 1.749) and a RD of -0.20 (95% CI -0.49 to 0.09). This is considered clinically relevant.

At day 14, the incidence was 0/15 in the intervention group, compared with 4/15 (26.7%) in the control group. This resulted in a RR of 0.11 (95% CI 0.01 to 1.90) and a RD of -0.27 (95% CI -0.50 to -0.03). This is considered clinically relevant.

Kyriazopoulou (2021) reported initiation of respiratory support in 4 categories. Results are provided in Table 2. The results are not considered clinically relevant.

Table 2. Results for the outcome respiratory support per category – mild and moderate disease.

Category	Intervention (n/N)	Control (n/N)	RR (95% CI)	RD (95% CI)
the need for high-flow oxygen or non-invasive ventilation	1/405	1/189	0.47 (0.03 to 7.42)	-0.01 (-0.01 to 0.01)
initiation of mechanical ventilation with P/F >150 mmHg	1/405	1/189	0.47 (0.03 to 7.42)	-0.01 (-0.01 to 0.01)
initiation of mechanical ventilation with P/F <150 mmHg or vasopressors	5/405	4/189	0.58 (0.16 to 2.15)	-0.01 (-0.03 to 0.01)
initiation of mechanical ventilation with P/F < 150 mmHg and vaso-pressors or haemodialysis or ECMO	6/405	6/189	0.47 (0.15 to 1.43)	-0.02 (-0.05 to 0.01)

Mariette (2021) reported number of patients needing non-invasive ventilation, mechanical ventilation or died

up to day 14. In the intervention group 28/59 (47.5%) achieved this outcome, compared with 28/55 (50.9%) in the control group. This resulted in a hazard ratio (HR; adjusted for age and centre) of 0.97 (95% CI 0.62 to 1.51).

By excluding the patients who died up to day 14, 19/50 (38.0%) patients in the intervention group, compared with 15/42 (35.7%) in the control group needed respiratory support. This resulted in a RR of 1.06 (95% CI 0.62 to 1.82) and a RD of 0.02 (95% CI -0.18 to 0.22). This is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of inconsistency (1 level, due to heterogeneity between the studies regarding medication and/or dose) and imprecision (2 levels, 95%CI of the mean difference includes no effect (RD=0), crosses both thresholds of clinical relevance, and low number of cases). The level of evidence for the outcome '*respiratory support*' is considered *very low*.

Duration of hospitalization (important)

Duration of hospitalization in hospitalized patients with COVID-19 was reported in three studies (Caricchio, 2021 Kyriazopoulou, 2021; Mariette, 2021). Caricchio (2021) and Mariette (2021) defined this outcome as the number of patients which discharged at day 29 and 28, respectively. Kyriazopoulou (2021) defined this outcome as time to hospital discharge in days. In addition, time of ICU stay was reported in this study. Declercq (2021) defined this outcome as median number of days in the hospital and ICU, respectively. Kharazmi (2021) defined this outcome as length of hospital stay and ICU length of stay.

Caricchio (2021) reported that 199/211 (94.3%) patients in the intervention group discharged at day 29, compared with 187/206 (90.8%) in the control group. This resulted in a RR of 1.04 (95% 0.98 to 1.10) and a RD of 0.04 (95%CI -0.02 to 0.09). This is not clinically relevant.

Declercq (2021) reported that the mean number of days in hospital was 19 (95% CI 17 to 22) in the intervention group (i.e., IL-1 blockade group), compared with 19 (95% CI 17 to 21) days in the control group (i.e., no IL-1 blockade group). This resulted in a mean difference of 0 days, which is not considered clinically relevant. Regarding the number of days at ICU, this was 11 (95% CI 8 to 15) in the intervention group, compared with 10 (95% CI 8 to 13) in the control group. This resulted in a mean difference of -1 day, which is not considered clinically relevant.

Kharazmi (2021) reported that the mean ($\pm$ SD) days of hospital stay was 9.5 ($\pm$ 4.5) in the intervention group (n=15), compared with 19 ($\pm$ 12) in the control group (n=15). This resulted in a mean difference of -9.5 days (95% CI -16 to -3). This is considered clinically relevant.

Regarding the length of stay at ICU, the mean ($\pm$ SD) in days was 5.5 ($\pm$ 2) in the intervention group, compared with 16.5 ($\pm$ 9) in the control group. This resulted in a mean difference of -11 days (95%CI -15.5 to -6.5). This difference is considered clinically relevant.

Kyriazopoulou (2021) reported the median (IQR) time in days, which was 11 (7.8) days, compared with 12 (8.5) days in the control group. The difference is 1 day, this is not considered clinically relevant. The median (IQR)

time of ICU stay was 10 (21) days in the intervention group, and 14 (22) days in the control groups. The difference is 4 days, this is considered clinically relevant.

Mariette (2021) reported that 34/59 (57.6%) patients in the intervention group discharged at day 28, compared with 34/55 (61.8%) in the control group. This resulted in a RR of 0.93 (95% CI 0.69 to 1.26) and a RD of -0.04 (95% CI -0.22 to 0.14). This is not clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels because of inconsistency (1 level, due to heterogeneity between the studies regarding medication and dose), and imprecision (1 level, 95%CI of the mean difference includes no effect [RD=0]). The level of evidence for the outcome '*duration of hospitalization*' is considered *low*.

Time to clinical improvement (important)

Time to clinical improvement in hospitalized patients with COVID-19 was reported in two studies (Cremer, 2021; Declercq, 2021).

Cremer (2021) reported the number of patients who achieved clinical improvement or discharge. This was defined as the time in days from randomization to either an improvement of two points on seven category ordinal scale or discharge from the hospital, whichever occurred first, at day 28. This was achieved in 14/15 (93.5%) of the patients in the intervention group, compared with 11/16 (68.8%) of the patients in the control group. This resulted in a RR of 1.36 (95% CI 0.95 to 1.94), and a RD of 0.25 (95% CI -0.01 to 0.51). This is considered clinically relevant.

Additional analysis 300 mg canakinumab

This was achieved in 11/14 (78.6%) of the patients in the intervention group, compared with 11/16 (68.8%) of the patients in the control group. This resulted in a RR of 1.14 (95% CI 0.74 to 1.75), and a RD of 0.10 (95% CI -0.21 to 0.41). This is considered clinically relevant.

Declercq (2021) reported the median (95% CI) time to clinical improvement in days. This was 12 (10 to 16) days in the intervention group (i.e., IL-1 blockade group), compared to 12 (10 to 15) days in the control group. This resulted in a HR of 0.94 (95% CI 0.73 to 1.21). The absolute difference of 0 days is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels because of risk of bias (1 level, selection bias might be present), and imprecision (2 levels, 95% CI of the mean difference includes no effect [HR=0, RD=0], crosses both thresholds of clinical relevance, and/or not meeting the optimal information size). The level of evidence for the outcome '*time to clinical improvement*' is considered *very low*.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with an interleukin (IL-)1 inhibitor compared to treatment without an interleukin (IL-)1 inhibitor in patients with COVID-19?

PICO

P: hospitalized with COVID-19 (subgroups mild, moderate, severe)

I: IL-1 inhibitor (i.e., anakinra or canakinumab) + standard care

C: standard care only / placebo treatment + standard care

O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

Relevant outcome measures

For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization, and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days difference for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and ICU admission (resulting in a NNT of 20).

Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 20 January 2022. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in indexed journal, comparing treatment with an IL-1 inhibitor and standard care to standard care alone or treatment with an IL-1 inhibitor and standard care to placebo and standard care in patients with COVID-19. Studies with $n < 10$ were excluded.

The systematic literature search resulted in 80.255 hits. Studies were further selected based on the following criteria: only systematic review or randomized controlled trials were included. Eventually, 5 studies were included. One additional study, which was not found by the literature search as the journal was not included in the databases, was included on request of the working group.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, six studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. Studies are presented in alphabetical order, only results of the primary outcome is reported in the summary of literature. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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JAK remmers

Uitgangsvraag

Wat is de plaats van Janus-geassocieerde kinasen (JAK) remmers bij de behandeling van COVID-19 patiënten?

Aanbeveling

Behandel opgenomen patiënten met respiratoire klachten door COVID-19 en een toegenomen zuurstofbehoefte met **tocilizumab 600 mg eenmalig i.v.** indien zij reeds zijn gestart met dexamethason **en** een CRP ≥ 75 mg/L hebben **en** een persisterend respiratoire verslechtering leidend tot noodzaak tot hoge zuurstofsuppletie - via een venturimasker (≥ 6 L O₂), non-rebreathing masker, NIV of high flow nasal oxygen (Optiflow) - met als meest aannemelijke verklaring de COVID-19 geïnduceerde longinflammatie (**niet** bijv. longembolieën of bacteriële pneumonie).

Behandel patiënten met respiratoire insufficiëntie die vanaf de SEH direct op de IC worden opgenomen (en daarom buiten het ziekenhuis al eerder aan de bovengenoemde criteria zouden hebben voldaan) naast dexamethason met tocilizumab. Hierbij wordt geadviseerd de therapie <24 uur na opname op de IC toe te dienen.

Indien tocilizumab niet beschikbaar is of dit om een andere reden niet gegeven kan worden, dan kan andere anti-inflammatoire therapie overwogen worden:

- **baricitinib** oraal **4 mg dagelijks gedurende 14 dagen of tot ontslag** of **sarilumab 400 mg i.v. eenmalig** (geen voorkeur uitgesproken voor een van beide middelen).

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in uitkomsten tussen behandeling met en zonder een Januskinase (JAK) remmer bij opgenomen en niet-opgenomen volwassenen met COVID-19. Tot 31 maart 2022 werden er 6 gerandomiseerde gecontroleerde studies (RCT's) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=1494 in de interventiegroep en n=1495 in de controlegroep). Er waren tot die tijd geen studies die systemische therapie met JAK remmers onderzochten in patiënten die niet waren opgenomen in het ziekenhuis. Een studie die inhalatie therapie met nezulcitinib (TD-0903) onderzocht, werd - vanwege de niet systemische toediening - wel gevonden in de search maar niet meegenomen in het daaropvolgende literatuur onderzoek. Dit onderzoek zal in de overige overwegingen kort besproken worden.

De geïnccludeerde studies onderzochten verschillende JAK remmers: ruxolitinib (Cao, 2020), tofacitinib (Guimaraes, 2021; Murugesan, 2021), baricitinib (Kalil, 2020; Marconi 2021; Ely, 2022). Dit is van belang omdat deze JAK-remmers niet allen precies dezelfde kinasen remmen, maar hoofdzakelijk bepaalde subtypes (JAK-1, JAK-2 en/of JAK-3). Er werden alleen RCT's geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. De kwaliteit van dit bewijs werd waar nodig naar beneden bijgesteld vanwege een grote spreiding van de puntschatter van de uitkomstmaat, beperkte patiëntaantallen (imprecisie) en/of

inconsistentie van de resultaten. De bewijskracht van de cruciale uitkomstmaten binnen patiënten die opgenomen waren in het ziekenhuis komt uit op 'redelijk' voor mortaliteit en 'laag' voor noodzaak tot uitgebreide respiratoire ondersteuning.

Studies in patiënten die waren opgenomen in het ziekenhuis

Op basis van de gevonden resultaten wordt er geconcludeerd dat er voor de cruciale uitkomstmaat 'mortaliteit' waarschijnlijk een klinisch relevante afname is bij het gebruik van JAK remmers. Voor de andere cruciale uitkomstmaat 'uitgebreide respiratoire ondersteuning' was het bewijs minder overtuigend. Zowel bij mortaliteit als bij de noodzaak tot respiratoire ondersteuning was er een statistisch significant voordeel te zien van behandeling met JAK remmers (pooled risk ratio voor mortaliteit 0.63, 95% CI 0.51 - 0.78, pooled risk ratio voor respiratoire ondersteuning 0.66, 95% CI 0.48-0.91). Dit effect bleek klinisch significant voor de uitkomstmaat mortaliteit, gebaseerd op de vooraf gedefinieerde grenzen van klinische significantie (>3 absolute procentpunten na gepoolde analyse). Het absolute risicoverschil van JAK remmers op respiratoire ondersteuning was 4% punten, want net onder de vooraf gedefinieerde grenzen van klinische significantie was (>5 absolute procentpunten na gepoolde analyse).

In de grootste geïncludeerde studie (Marconi, 2021) was het voordeel van de JAK remmer baricitinib op de mortaliteit 5% punten (statistisch significant), dit was een secundaire uitkomstmaat van de studie. In deze multicenter placebo gecontroleerde RCT werden 1525 patiënten gerandomiseerd naar standaardzorg plus baricitinib 4 mg 1dd of standaardzorg. De 28 dagen en 60 dagen mortaliteit (secundaire uitkomstmaten) lagen statistisch significant lager in de groep die was behandeld met baricitinib (28 dagen mortaliteit 8% versus 13% (HR 0.57; CI 95% 0.41-0.78)). Circa 90 procent van de patiënten werd ook behandeld met dexamethason, maar ook andere behandelingen, zoals remdesivir, waren toegestaan. Een belangrijk deel van de patiënten (>80%) startte met baricitinib >7 dagen na start symptomen.

Het is op dit moment niet duidelijk hoe JAK remmers zoals baricitinib zich verhouden tot andere anti-inflammatoire therapieën. In de RCT's van Marconi, Guimaraes, Cao en Ely gebruikten >70% van de patiënten ook corticosteroïden, waardoor een klein additioneel voordeel van JAK remmers aannemelijk lijkt. In geen van de studies werd echter een combinatie met IL-6 remmers of IL-1 remmers gebruikt of werd er gerandomiseerd naar JAK of IL-6 of IL-1 remming, waardoor de plaats van JAK remmers ten opzichte van deze middelen onduidelijk blijft. Een combinatie van een JAK remmer en bijvoorbeeld tocilizumab (IL-6 remmer) wordt ontraden vanwege het veronderstelde hogere risico op secundaire infecties.

Daarnaast is het nog niet duidelijk in welk ziektestadium of bij welke inflammatiemarkers (CRP, ferritine) er het meest effect van JAK remming te verwachten valt. Het grootste effect van antivirale therapie wordt met name vroeg verwacht, terwijl het anti-inflammatoire effect later in het ziektebeloop wordt verwacht. Aangezien JAK remmers zoals baricitinib en tofacitinib beide eigenschappen bezitten, kan de timing van deze toediening belangrijk zijn. In de studies in deze richtlijn werden patiënten relatief laat behandeld: gemiddeld 20 dagen na het ontstaan van symptomen bij de studie van Cao (2020), gemiddeld 10 dagen bij Guimaraes (2021) en 8 dagen bij Kalil (2020). Bij Marconi (2021) en Ely (2022) startte een belangrijk deel van de patiënten (>80%) met baricitinib meer dan 7 dagen na start symptomen en alle geïncludeerde patiënten bij Marconi hadden minimaal 1 verhoogde inflammatiewaarde. In subgroep analyses van Guimaraes (2021) en Kalil (2020) werd er geen overtuigend bewijs gezien dat behandeling met een JAK remmer vroeger of later in

het beloop een verschil maakte. Wel toonde de studie van Kalil (2020) dat er een snellere klinische verbetering was in een subgroep van patiënten die bij randomisatie non-invasieve beademing kregen. Dit voordeel werd niet gezien bij patiënten die lagen opgenomen met mechanische ventilatie. In de huidige richtlijn werd een subgroep analyse gedaan waarin patiënten werden gestratificeerd naar ernst van ziekte. Een gepoolde analyse van de studies van Kalil (2020), Marconi (2021), Guimaraes (2021) en Ely (2022) liet consequent een voordeel gezien van JAK remming bij patiënten met zuurstof op de afdeling (matig ernstige ziekte) en bij patiënten met invasieve respiratoire ondersteuning (ernstige ziekte).

Soort JAK remmer

Drie van de zes geïnccludeerde trials bestudeerden baricitinib, waaronder de twee grootste RCT's, waardoor binnen de categorie JAK remmers er een voorkeur wordt uitgesproken voor baricitinib.

Combinatietherapie of monotherapie

De Engelse en Amerikaanse richtlijnen spraken eerder een voordeel uit voor combinatietherapie van een JAK remmer met bijvoorbeeld remdesivir. Deze aanbeveling werd gedaan toen de studie van Kalil (2020) het grootste bewijs vormde in het voordeel van baricitinib. Echter, ook baricitinib zonder een andere virusremmer lijkt effectief in het verlagen van de mortaliteit (Marconi, 2021). Wel is combinatietherapie met dexamethason aan te bevelen. Data over de combinatie van JAK remmers met andere anti-inflammatoire therapie (anders dan corticosteroïden) zoals IL-6 remmers is op dit moment niet aanwezig. Een dergelijke combinatietherapie wordt dan ook niet aanbevolen buiten studieverband.

Studies in ambulante patiënten

Er werden geen studies gevonden die JAK-remmers vergeleken met placebo in niet-opgenomen volwassenen met COVID-19.

Overige overwegingen

Bijwerkingen

Een meta-analyse die de bijwerkingen JAK remmers bekeek tijdens behandeling van reumatoïde artritis, toonde dat behandeling met JAK remmers geassocieerd was met een hoger infectierisico (met name reactivatie van herpes virussen) en toonde een mogelijke associatie met: cardiovasculaire problematiek waaronder veneuze trombo-embolische complicaties, gastro-intestinale perforatie en maligniteit (Honda, 2020; Peng, 2020). Het risico op bijvoorbeeld (ernstige) infecties verschilde per JAK remmer (Bechman, 2019). Bijwerkingen die gezien worden bij een langdurige behandeling met JAK remmers, zoals bij bovengenoemde chronische ziekte, zijn mogelijk anders dan de bijwerkingen die gezien kunnen worden bij COVID-19 behandeling, waarbij patiënten maximaal 14 dagen werden behandeld. In de RCT's in deze richtlijn werd er ook gekeken naar bijwerkingen van JAK remmers ten opzichte van placebo. De meest voorkomende 'serious adverse events' waren een verhoging van de leverenzymen (ALT) of het ontstaan van een lymfopenie (Guimaraes, 2021). In geen van de studies werden er meer bijwerkingen gezien in de interventie groep vergeleken met placebo. Ook als er specifiek gekeken werd naar infectieuze complicaties (Marconi, 2021; Cao, 2021; Guimaraes, 2021; Ely, 2022), werden deze niet meer gezien vergeleken met de placebogroep.

Virusvarianten

Sinds de opkomst van de omikron variant van SARS-CoV-2 in Nederland eind 2021, is de kans op een ernstig beloop van COVID-19 op populatieniveau zeer sterk gedaald. Het is van belang om op te merken dat de besproken gerandomiseerde studies werden verricht voor de opkomst van de omikron variant. Het is onduidelijk wat de invloed is van deze variant op het effect van anti-inflammatoire therapie, al wordt aangenomen dat patiënten die door de omikron variant een ernstige COVID-19 infectie ontwikkelen nog steeds baat hebben bij anti-inflammatoire therapie. De 'number needed to treat' zou wel anders (vermoedelijk hoger) kunnen zijn.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens kunnen JAK remmers worden ingezet in de behandeling van COVID-19. In de behandeling van COVID-19, waar deze middelen relatief kortdurend worden voorgeschreven, werden er wel voordelen van JAK remmers gevonden (zoals een lagere mortaliteit), maar werden er niet meer bijwerkingen gezien. Mogelijk zijn de patiënten aantallen nog niet groot genoeg om alle bijwerkingen in de behandeling van COVID-19 aan te tonen. Een potentieel verhoogd risico op infecties of andere bijwerkingen die bij de behandeling van bijvoorbeeld reumatoïde artritis gezien werden, moet dus meegewogen worden in de keuze om een patiënt met een JAK remmer te behandelen. Deze potentiële bijwerkingen spelen overigens ook een rol bij andere anti-inflammatoire middelen die ingezet kunnen worden bij COVID-19.

Kosten (middelenbeslag)

In de huidige studies varieert de gebruikte JAK remmer en de duur van de behandeling. In de grootste studie van Marconi (2021) werd 4mg baricitinib gedurende 14 dagen voorgeschreven. De kosten die met deze behandeling gepaard gaan zijn ongeveer 400-500 euro. Hierin zijn niet de opname in het ziekenhuis of andere bijkomende kosten meegenomen.

Aanvaardbaarheid, haalbaarheid en implementatie

Op grond van de bekende onderzoeksgegevens kunnen JAK remmers worden ingezet in de behandeling van COVID-19. Baricitinib is beschikbaar in Nederland en patiënten die in aanmerking komen voor deze behandeling liggen opgenomen in het ziekenhuis. De werkgroep voorziet geen problemen qua implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Gebaseerd op de RCT's in deze richtlijn wordt er geconcludeerd dat behandeling met JAK-remmers (in het bijzonder baricitinib) waarschijnlijk zorgt voor een klinisch relevante afname van de mortaliteit binnen 28 dagen vergeleken met placebobehandeling bij opgenomen patiënten met COVID-19.

Het mortaliteits-voordeel van JAK remming is met name bestudeerd in een (matig) ernstig zieke populatie, waar ook bewijs is voor een meerwaarde van IL-6 remming (in het bijzonder tocilizumab). Van beide soorten middelen beschrijven RCT's geen significante bijwerkingen bij behandeling van COVID-19, al betreft dit een relatief korte follow-up.

Het verwachte effect en de bewijskracht van de literatuur betreffende het effect van baricitinib en tocilizumab op mortaliteit is vergelijkbaar, vooral als er niet alleen gekeken wordt naar de 28 dagen mortaliteit maar ook andere follow-up duur. Er is meer ervaring met tocilizumab in de behandeling van COVID-19 in Nederland en

dit middel werd in grotere aantallen patiënten onderzocht: 12 RCT's onderzochten bij ruim 7000 patiënten het effect van tocilizumab, 3 RCT's onderzochten bij ruim 2500 patiënten baricitinib. In patiënten met een (matig) ernstige COVID-19 infectie wordt er daarom een voorkeur uitgesproken voor tocilizumab.

Behandeling met JAK-remmers, in het bijzonder baricitinib, zorgt waarschijnlijk voor een klinisch relevante afname van de mortaliteit binnen 28 dagen bij een geselecteerde groep ((matig) ernstig zieke populatie) opgenomen patiënten met COVID-19. In deze groep is er ook een voordeel te zien IL-6 remmers, in het bijzonder bij tocilizumab. Op basis van bovenstaande bewijs is het advies:

Onderbouwing

Achtergrond

Een infectie met SARS-CoV-2 kan leiden tot een ernstige pneumonie en ARDS. Een dysregulatie van de immuunrespons lijkt in de pathofysiologie van COVID-19 een belangrijke rol te spelen (Veerdonk, 2022). Janus-geassocieerde kinasen (JAK) remmers kunnen worden gebruikt om cel proliferatie te remmen maar ook als anti-inflammatoire therapie, zoals bij reumatoïde artritis en eczeem. Een Italiaanse observationele studie toonde een significante reductie van de hoeveelheid inflammatoire cytokines, een toename van de circulerende B- en T-cellen en een toegenomen antistof productie tegen het SARS-COV-2 spike eiwit bij 20 patiënten met een ernstige COVID-19 die met de JAK remmer baricitinib werden behandeld (Bronte, 2020). Daarnaast lijken baricitinib en ruxolitinib ook een antiviraal effect te hebben, door remming van de endocytose van SARS-CoV-2 (Gatti, 2021; Richardson, 2020).

Inmiddels hebben diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit van JAK remmers onderzocht om de plaats van deze middelen bij de behandeling COVID-19 te bepalen. Klinische dose-finding studies zijn in deze setting nooit verricht. De groep JAK remmers uit dit literatuuronderzoek bevat meerdere middelen: baricitinib en ruxolitinib (JAK 1 en JAK 2 remmers) en tofacitinib (JAK 1/3 remmer met mogelijk ook werking tegen JAK 2). Alleen systemische middelen werden bij het literatuuronderzoek meegenomen. Inhalatie therapie met JAK remmers (zoals nezulcitinib) zal kort in de overwegingen worden besproken.

Conclusies / Summary of Findings

Hospitalized patients

Mortality (crucial)

Moderate GRADE	Treatment with a JAK inhibitor probably reduces mortality when compared with treatment without a JAK inhibitor in <u>hospitalized</u> patients with COVID-19. Source: Cao, 2020; Ely, 2022; Guimarães, 2021; Kalil, 2020; Marconi, 2021.

Extensive respiratory support (crucial)

Low GRADE	Treatment with a JAK inhibitor may result in limited difference in need for extensive respiratory support when compared with treatment without a JAK inhibitor in <u>hospitalized</u> patients with COVID-19. <i>Source: Cao, 2020; Guimarães, 2021; Kalil, 2020.</i>

Duration of hospitalization (important)

Low GRADE	Treatment with a JAK inhibitor may result in little to no difference in length of stay when compared with treatment without a JAK inhibitor in <u>hospitalized</u> patients with COVID-19. <i>Source: Cao, 2020; Ely, 2022; Guimarães, 2021; Marconi, 2021.</i>

Time to clinical improvement (important)

Moderate GRADE	Treatment with a JAK inhibitor probably results in little to no difference in time to clinical improvement when compared with treatment without a JAK inhibitor in <u>hospitalized</u> patients with COVID-19. <i>Source: Kalil, 2020; Marconi, 2021.</i>

Non-hospitalized patients

- GRADE	No conclusions can be drawn about the comparison of treatment with a JAK inhibitor with treatment without a JAK inhibitor in non-hospitalized patients, because no studies were found that reported relevant outcomes for the comparison.

Samenvatting literatuur

Description of studies

Cao (2020) performed a prospective, multicenter, single-blind, randomized controlled phase II trial, which was conducted in China. They evaluated clinical improvement by comparing ruxolitinib plus standard of care treatment or placebo based on standard of care treatment in hospitalized adults with severe COVID-19. In total 43 were included as they met the criteria (i.e., met the diagnostic criteria for COVID-19; were 18 years or older and younger than 75 years; were severely cases according to the Chinese management guideline for COVID-19 version 5.0. These patients were randomized to receive ruxolitinib (n=22) or placebo (n=21), both with standard of care. After randomization, 2 patients were excluded from the ruxolitinib group because 1 was found to be ineligible because of persistent humoral immune deficiency after B-cell mature antigen-targeting chimeric antigen receptor T-cell therapy, while another withdrew the consent before treatment started. Placebo treatment included 100mg vitamin C twice a day. Standard of care included antiviral therapy, supplemental oxygen, non-invasive and invasive ventilation, corticosteroids (in 70% of the patients), antibiotic agents, vasopressor support, renal-replacement therapy, and extracorporeal membrane oxygenation. The mean age was 63 years, and 59% were male. The length of the follow-up was 28 days. The following outcome measures were reported; mortality, need for respiratory support, and duration of

hospitalization. The primary efficacy end point was the time to clinical improvement. No statistical differences were detected in terms of clinical improvement between the 2 groups. The study had a high risk of bias for outcomes directly related to treatment decisions, as treating physicians were aware of group allocations.

Ely (2022) reported efficacy and safety of baricitinib in a critically ill cohort not previously included in the **COV-BARRIER trial**. In this multicentre, randomised, double-blind, placebo-controlled, parallel-group trial, participants were enrolled across 18 centres in four countries. Eligible patients were those aged 18 years or older, who had been hospitalised with laboratory-confirmed SARS-CoV-2 infection, with use of IMV or ECMO at study entry and randomisation, evidence of pneumonia or clinical symptoms of COVID-19, and indicators of progression risk with at least one elevated inflammatory marker greater than the upper limit of normal range based on the local laboratory result (C-reactive protein, D-dimer, lactate dehydrogenase, or ferritin). Baricitinib 4 mg (N=51) or matched placebo (N=50) was crushed for nasogastric tube delivery (or given orally when feasible) and given once daily for up to 14 days or until discharge from hospital, whichever occurred first. Participants assigned to baricitinib with baseline estimated glomerular filtration rate (eGFR) of 30 to less than 60 mL/min per 1.73 m² received baricitinib 2 mg or matched placebo. If eGFR decreased to 30 to less than 60 mL/min per 1.73 m² after randomisation, patients received baricitinib 2 mg until eGFR returned to 60 mL/min per 1.73 m² or greater. All participants received standard of care in keeping with local clinical practice for COVID-19 management, which could include concomitant medications such as corticosteroids (84% in the baricitinib group, 88% in the control group), antivirals (remdesivir 0% in the baricitinib group, 4% in the control group). The prespecified key endpoints for this exploratory trial were all-cause mortality at day 28 and day 60; number of ventilator-free days; overall improvement (assessed by odds of improvement in clinical status) on NIAID-OS, evaluated at days 4, 7, 10, 14, and 28; proportion of participants with at least 1-point improvement on the NIAID-OS or live discharge from hospital at days 4, 7, 10, 14, and 28; duration of hospitalisation; and time to recovery through day 28. As the cohort reported here was an addition to the parent trial study design (COV-BARRIER), all endpoints are considered exploratory. Primary endpoints were not defined.

Guimarães (2021) (STOP-COVID trial) performed a randomized controlled phase II trial, which was conducted in Brazil. They evaluated effectiveness of tofacitinib, compared with placebo plus standard care in hospitalized adults with COVID-19 pneumonia. In total 289 were included as they met the criteria (i.e., 18 years of age or older who had laboratory-confirmed SARS-CoV-2 infection, who had evidence of COVID-19 pneumonia on radiographic imaging (computed tomography or radiography of the chest), and who had been hospitalized for less than 72 hours). These patients were randomized to receive tofacitinib (n=144) or placebo (n=145), both in addition to standard of care. Placebo treatment included oral placebo twice a day. Standard of care included glucocorticoids (89%), antibiotic agents, anticoagulants, and antiviral agents. The mean age was 56 years, and 56% were male. The length of the follow-up was 28 days. The following outcome measures were reported; mortality, need for respiratory support, and duration of hospitalization. The primary outcome was the occurrence of death or respiratory failure through day 28 as assessed with the use of an eight-level ordinal scale (with scores ranging from 1 to 8 and higher scores indicating a worse condition). The cumulative incidence of death or respiratory failure through day 28 was 18.1% in the tofacitinib group and 29.0% in the placebo group (risk ratio, 0.63; 95% confidence interval (CI), 0.41 to 0.97; P= 0.04).

Kalil (2020) (ACTT-2 trial) performed a double-blind, randomized, placebo-controlled trial, which was

conducted in USA, Singapore, South Korea, Mexico, Japan, Spain, UK and Denmark. They evaluated effectiveness of remdesivir and baricitinib or placebo, both in addition to standard care in hospitalized adults with COVID-19. In total 1033 were included as they met the criteria (i.e., hospitalized male or non-pregnant female adults with moderate to severe COVID-19). These patients were randomized to receive baricitinib plus remdesivir (n=518) or placebo and remdesivir (n=518), both in addition to standard of care. Venous thromboembolism prophylaxis was recommended for all the patients without a major contraindication as standard of care. If a hospital had a written policy for Covid-19 treatments, patients could receive those treatments. The mean age was 55 years, and 53% were male. The length of the follow-up was 29 days. The following outcome measures were reported; mortality, and need for respiratory support. The primary outcome was the time to recovery. Patients receiving baricitinib had a median time to recovery of 7 days (95% confidence interval (CI), 6 to 8), as compared with 8 days (95% CI, 7 to 9) with control (rate ratio for recovery, 1.16; 95% CI, 1.01 to 1.32; P = 0.03).

Marconi (2020) (COV-BARRIER trial) performed a multicentre, randomised, double-blind, placebo-controlled, parallel-group, phase 3 trial, which was conducted in 12 countries in Asia, Europe, North America and South America. They evaluated effectiveness of baricitinib 4mg during 14 days, compared with placebo in hospitalized adults with symptomatic COVID-19 with ≥ 1 inflammatory marker. In total 1525 were included as they met the criteria (i.e., at least 18 years of age, hospitalised with laboratory-confirmed SARS-CoV-2 infection, evidence of pneumonia or active and symptomatic COVID-19, and with at least one elevated inflammatory marker (C-reactive protein, D-dimer, lactate dehydrogenase, or ferritin). These patients were randomized to receive baricitinib (n=764) or placebo (n=761), both in addition to standard of care (i.e., local clinical practice for COVID-19 management, which could include corticosteroids (91% of the patients used dexamethasone), antivirals, or both; dexamethasone use was permitted as described in the RECOVERY trial). The mean age was 58 years, and 63% were male. The length of the follow-up was 28 days. The following outcome measures were reported; mortality, and duration of hospitalization. The composite primary endpoint was the proportion who progressed to high-flow oxygen, non-invasive ventilation, invasive mechanical ventilation, or death by day 28, assessed in the intention-to-treat population. Overall, 27.8% of participants receiving baricitinib and 30.5% receiving placebo progressed to meet the primary endpoint (odds ratio 0.85 (95% CI 0.67 to 1.08), p=0.18), with an absolute risk difference of -2.7 percentage points (95% CI -7.3 to 1.9).

Murugesan (2021) performed an open-label randomized study to test efficacy and safety of tofacitinib in hospitalized patients with mild to moderate COVID-19. The study was conducted in India. Hospitalized patients in the age group of 18 - 65 years, diagnosed positive for SARS-CoV2 infection by RT-PCR and radiological imaging (Chest X-ray or CT scan) confirmed pneumonia with lower respiratory tract infection features indicating moderate pneumonia, were randomized to receive oral tofacitinib (10 mg PO BID for 14 days) and standard of care (N=50) or standard of care alone (N=50), which included e.g. remdesivir (98%), and corticosteroids (dexamethasone 85%, methylprednisolone 15%). The mean age was 58 years, and 63% were male. The length of the follow-up was 28 days. Primary outcomes were the proportion of patients not requiring any form of mechanical ventilation or high flow oxygen or ECMO at day 7 or mortality. The proportion of population requiring oxygen supplementation was similar in both the groups (28% in the tofacitinib group, 26% in the control group, P=0.82). There was no mortality in either group.

Table 1. Overview of RCTs comparing JAK inhibitors with standard care in hospitalized COVID-19 patients.

Author	Disease severity, based on need for respiratory support*	Sample size	Intervention	Control
Cao, 2020	Mixed moderate/severe, not further specified.	I: N=20 C: N=21 Total: N=41	Patients allocated to the active drug received an oral dose of 5mg ruxolitinib twice a day plus standard of care	Placebo (100mg vitamin C) twice a day plus standard-of-care.
Ely, 2022 Critically ill cohort not included in the COV-BARRIER trial	Severe disease: I: 100% C: 100%	I: N=51 C: N=50 Total: N=101	Patients allocated to the active drug received baricitinib 4 mg crushed for nasogastric tube delivery (or given orally when feasible) and given once daily for up to 14 days or until discharge from hospital, whichever occurred first.	Placebo.
Guimarães, 2021 STOP-COVID trial	Mixed mild to severe: I: mild: 23.6% moderate: 63.2% severe: 13.2% C: mild: 25.5% moderate: 63.2% severe: 12.4% (Defined by NIAID ordinal scale)	I: N=144 C: N=145 Total: N=289	Patients allocated to the active drug received an oral dose of 10 mg tofacitinib twice daily for up to 14 days or until hospital discharge, whichever was earlier.	Oral placebo twice daily.

Kalil, 2020 ACTT-2 trial	Mixed mild to severe: I: mild: 13.6% moderate: 55.9% severe: 30.5% C: mild: 13.9% moderate: 53.5% severe: 32.8% Need for supplemental oxygen, mechanical ventilation, or extracorporeal membrane oxygenation were criteria for inclusion.	I: N=515 C: N=518 Total: N=1033	Patients allocated to the active drug received remdesivir and baricitinib: 4-mg daily dose (either orally or through a nasogastric tube) for 14 days or until hospital discharge or death.	Remdesivir and placebo.
Marconi, 2021 COV-BARRIER trial	Mixed mild to severe: I: mild: 12% moderate: 64% severe: 24% C: mild: 13% moderate: 62% severe: 25%	I: N=764 C: N=761 Total: N=1525	Patient allocated to the active drug received a dose of baricitinib 4 mg/day (oral) for up to 14 days or until hospital discharge; 2 mg/day if eGFR at baseline was 30-60 mL/min per 1.73 m².	Placebo.
Murugesan, 2021	Mild to moderate, not further specified	I: N=50 C: N=50 Total: N=100	Patients allocated to the active drug received oral tofacitinib, 10 mg PO BID for 14 days plus standard of care.	Standard of care treatment alone.

**Disease severity categories:*

- *mild disease (no supplemental oxygen);*
- *moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);*
- *severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).*

N: Total sample size; I: Intervention; C: Control

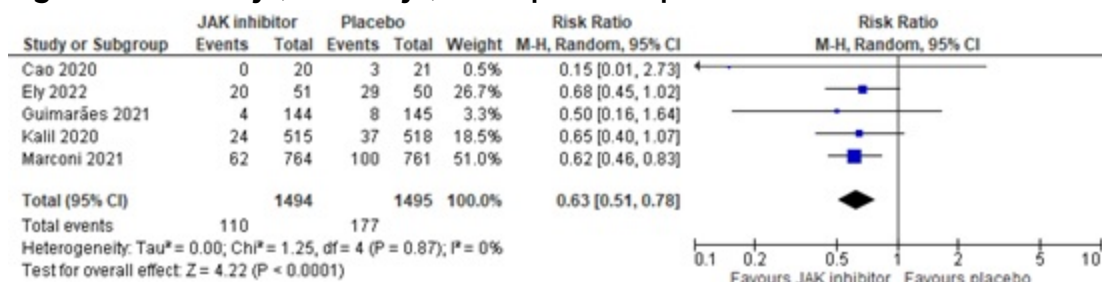
Results – Hospitalized patients

Since the number of studies and the number of patients included was relatively limited, we report all outcomes for the different JAK inhibitors combined. Also conclusions were reported for all JAK inhibitors combined.

Mortality (crucial)

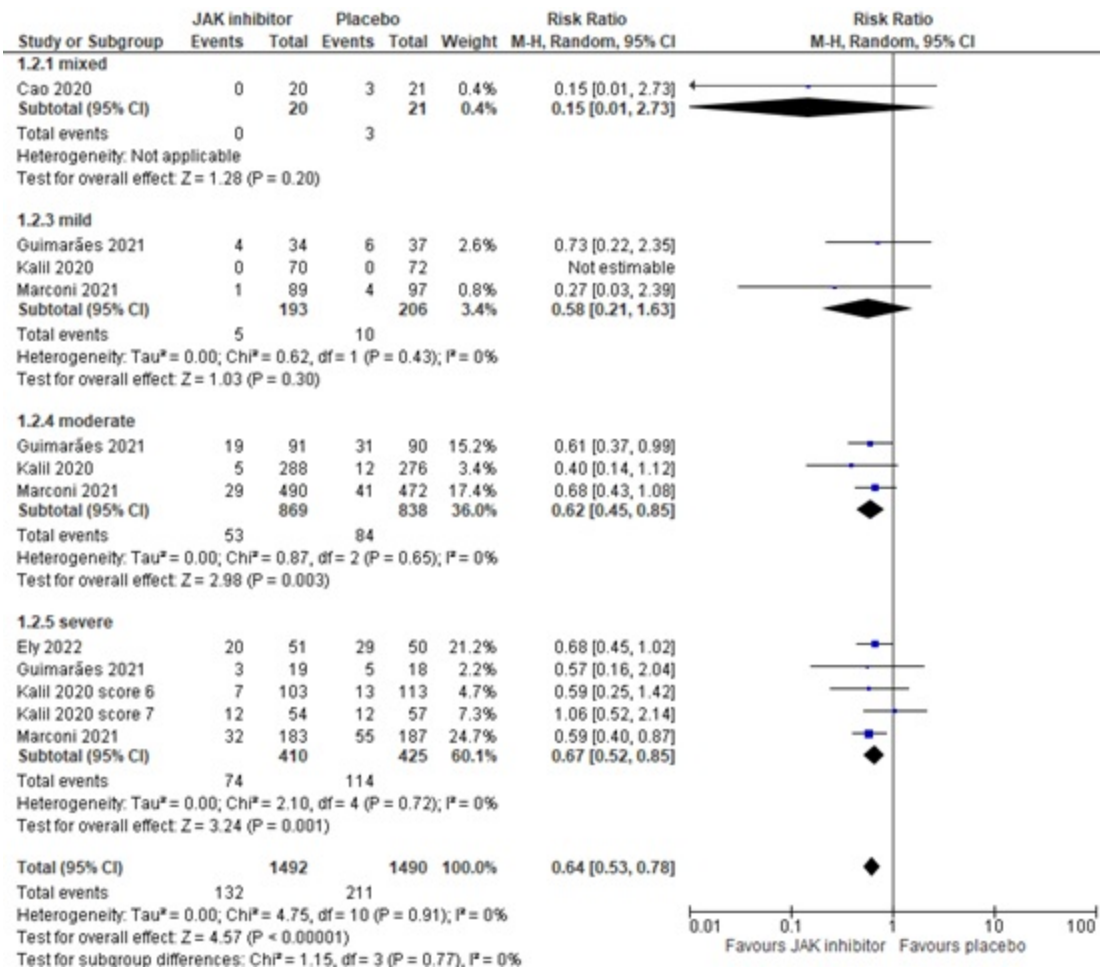
Five studies reported mortality at 28 days. In all hospitalized patients with COVID-19, the pooled 28-day mortality in the JAK inhibitor group was 110/1494 (7.4%), compared to 177/1495 (11.8%) in the control group. The pooled risk ratio (RR) was 0.63 with a 95% confidence interval (CI) from 0.51 to 0.78, in favour of the intervention group (figure 1). The pooled risk difference (RD) was -0.041 (95% CI -0.068 to 0.014), in favour of the intervention group. This is considered clinically relevant. Murugesan (2021) did not report mortality at 28 days, but found no mortality in either group (both N=50) at day 14. Figure 2 presents mortality grouped by disease severity at baseline. Of note, there is a slight discrepancy in the reported patient numbers for the subgroups (figure 2) and the total study populations (Figure 1).

Figure 1: Mortality (28-30days) in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; τ^2 : statistical heterogeneity; CI: confidence interval.

Figure 2: Mortality (28-30days) in hospitalized patients by disease severity



Z: p-value of overall effect; df: degrees of freedom; ²: statistical heterogeneity; CI: confidence interval.

Level of evidence of the literature

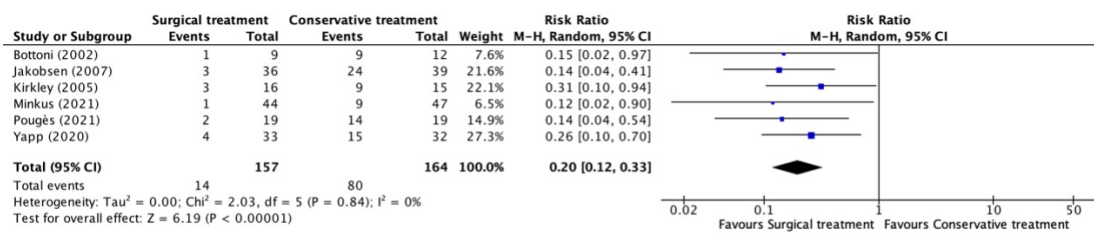
The level of evidence for all outcomes was based on randomized studies and therefore starts at high. For the outcome mortality, the level of evidence was downgraded by 1 level to moderate because the pooled confidence interval crossed the limit of clinical decision making (imprecision, -1).

Extensive respiratory support (crucial)

Three studies reported the need for invasive respiratory support (invasive mechanical ventilation or EMCO, NIAID score 7). In hospitalized patients with COVID-19, the pooled need for mechanical respiratory support in the JAK inhibitor group was 53/625 (8.5%), compared to 82/627 (13.1%) in the control group. The pooled RR was 0.66 (95% CI 0.48 to 0.91) in favour of the intervention group (figure 3).

The pooled risk difference (RD) was -0.042 (95% CI -0.085 to 0.001), in favour of the intervention group. This is not considered clinically relevant.

Figure 3: Need for extensive respiratory support in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; τ^2 : statistical heterogeneity; CI: confidence interval.
From the study by Guimarães (2021, STOP-COVID trial), values at day 14 were used.

Marconi (2021) did not report need for respiratory support in the COV-BARRIER trial, but reported the number of ventilator-free days, and found least square means (standard error) of 24.5 (0.39) days for the baricitinib group ($n=764$) versus 23.7 (0.39) in the placebo group ($n=761$). Similarly, Ely (2022) reported a mean (standard error) ventilator-free days of 8.1 (10.2) in the baricitinib group versus 5.5 (8.4) in the placebo group ($P=0.21$).

Three studies reported the need for non-invasive ventilation or high-flow oxygen devices (NIAID score 6). In the STOP-COVID trial, 1/144 patients (0.7%) in the JAK inhibitor treated group needed non-invasive ventilation versus 6/145 (4.1%) in the placebo group. In the ACTT-2 trial, 70/358 (19.6%) patients treated with JAK inhibitors needed non-invasive ventilation or high-flow oxygen versus 82/348 (23.6%) in the placebo group. Cao (2020) reported 2/20 (10%) patients in the JAK group who needed non-invasive respiratory support versus 4/21 (19.0%) in the placebo group. Taken together, 73/522 (14.0%) patients receiving JAK inhibitors needed non-invasive ventilation versus 92/514 (17.9%) in the placebo group. The pooled RR was 0.77 (95% CI 0.59 to 1.02) in favour of the intervention group (figure 3). The pooled RD was -0.037 (95% CI -0.067 to 0.007) in favour of the intervention group. This is not considered clinically relevant.

Three studies reported need for supplemental oxygen (NIAID score 5). The STOP-COVID trial by Guimarães (2021) reported 7/144 (4.9%) patients receiving supplemental oxygen through low-flow devices of at day 14 in the tofacitinib group, versus 6/145 (4.1%) in the placebo group in patients with mild to severe COVID-19. The ACTT-2 trial (Kalil, 2020) reported 16/70 (22.9%) patients receiving new use of oxygen during the trial in the baricitinib group versus 29/72 (40.3%) in the placebo group (both groups also received remdesivir) in patients with mild to severe COVID-19. Murugesan reported that the proportion of population requiring oxygen supplementation (not further specified) was similar in both groups (28% in the tofacitinib group versus 26% in the control group, $P=0.82$).

Level of evidence of the literature

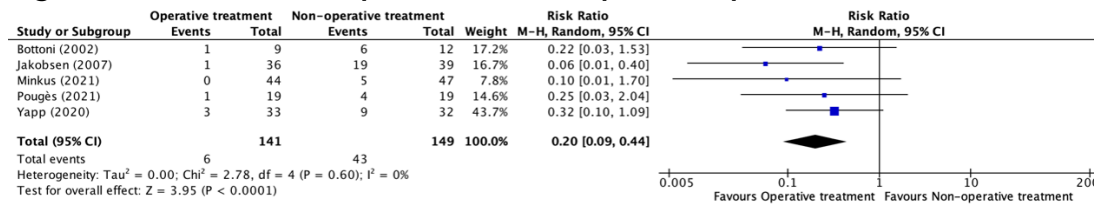
The level of evidence for all outcomes was based on randomized studies and therefore starts at high. For the outcome need for extensive respiratory support, the level of evidence was downgraded with 2 levels to LOW because the confidence interval crossed the limit of clinical decision making and because number of included patients was limited (both imprecision, -2).

Duration of hospitalization (important)

Five studies reported hospital length of stay. The mean difference was -1.06 days, with a 95% CI from -1.81 to -0.31 in favour of JAK inhibitor treatment (figure 4). The difference is not considered clinically relevant. Murugesan did not report the data, but stated that there were no differences in duration of hospitalization

between the groups.

Figure 4: Duration of hospitalization in hospitalized patients



Z: p-value of overall effect; **df:** degrees of freedom; **τ^2 :** statistical heterogeneity; **CI:** confidence interval.

Level of evidence of the literature

The level of evidence for all outcomes was based on randomized studies and therefore starts at high. For the outcome hospital length of stay, the level of evidence was downgraded with 2 levels to LOW due to conflicting results (inconsistency, -1), and due to the limited number of included patients (imprecision, -1).

Time to clinical improvement (important)

Three studies reported time to recovery. Marconi (2021) reported a median (95% CI) time to recovery (NIAID-OS score of 1-3) of 10.0 (9.0-11.0) days for baricitinib versus 11.0 (10.0-12.0) for placebo in 1525 hospitalized patients with mild to severe COVID-19. The difference was not considered clinically relevant.

Kalil (2020) reported median (95% CI) time to recovery (the first day, on which a patient attained category 1, 2, or 3 on the eight-category ordinal scale) for baricitinib versus placebo (both groups included additional remdesivir treatment), and found 7 (6-8) versus 8 (7-9) for all 1033 hospitalized patients with COVID-19, 5 (4-6) versus 4 (4-6) in 142 hospitalized patients with mild COVID-19, 5 (5-6) versus 6 (5-6) in 564 hospitalized patients with moderate COVID-19, and 10 (9-13) versus 18 (13-21) in 216 hospitalized patients with severe COVID-19. Only for the last category, the difference was considered clinically relevant. For patients with severe COVID-19 receiving invasive mechanical ventilation or EMCO at baseline, time to recovery could not be estimated.

Ely (2022) investigated time to recovery, but this was not reported at 28 days follow-up. There was no significant difference in the proportion of participants who had recovered at day 60 in the baricitinib group compared with the placebo group: 47% versus 32%.

Level of evidence of the literature

The level of evidence for all outcomes was based on randomized studies and therefore starts at high. For the outcome clinical improvement, the level of evidence was downgraded with 1 level to MODERATE due to the limited number of included patients (imprecision, -1).

Non-hospitalized patients

No randomized studies were found that compared JAK inhibitor treatment with placebo treatment in non-hospitalized patients.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of Januskinase (JAK) inhibitor treatment compared to treatment without a Januskinase (JAK) inhibitor in patients with COVID-19?

PICO

PICO 1

P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
 I: JAK inhibitor (systemic) + standard care
 C: standard care only / placebo treatment + standard care
 O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

P: non-hospitalized patients with COVID-19
 I: JAK inhibitor (systemic) + standard care
 C: standard care only / placebo treatment + standard care
 O: 28-30 day mortality (if not available, other follow-up), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization, and time to clinical improvement were considered as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days difference for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and ICU admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);

- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until March 31, 2022. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 686 hits. Studies were selected based on the following criteria: randomized controlled trial with at least 10 patients per arm, peer reviewed and published in indexed journal or pre-published, comparing treatment with a JAK inhibitor with placebo or usual care in adult patients with COVID-19.

The systematic literature search resulted in 82001 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials. Eventually, six studies were included.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

Six studies were included in the analysis of the literature. Five studies compared a JAK inhibitor with placebo in hospitalized adult COVID-19 patients, the study of Murugesan (2021) was an open-label trial. Important study characteristics and results are summarized below. Studies are presented in alphabetical order, only results of the primary outcome is reported in the summary of literature. Additionally, studies are summarized in the evidence tables. The assessment of the risk of bias is summarized separately in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Ivermectine

Uitgangsvraag

Wat is de plaats van ivermectine bij de behandeling van COVID-19 patiënten?

Aanbeveling

Ivermectine wordt niet aanbevolen als behandeling van patiënten met COVID-19

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder ivermectine bij patiënten opgenomen in het ziekenhuis met COVID-19 en patiënten niet opgenomen in het ziekenhuis. Tot 7 april 2022 werden er 17 gerandomiseerde gecontroleerde studies (RCT's) gevonden. Tien studies onderzochten het effect van behandeling met ivermectine in patiënten met COVID-19 die waren opgenomen in het ziekenhuis en zeven studies werden uitgevoerd in patiënten die niet waren opgenomen in het ziekenhuis.

Er werden alleen RCT's geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. De geïnccludeerde studies hadden in wisselende mate methodologische beperkingen (risk of bias). Er was in sommige studies een risico op bias door onder andere ontoereikende documentatie, lost of follow-up en missende data, of de gebruikte statistische analyse (risk of bias). Daarnaast waren de studiebevindingen onderling inconsistent (inconsistency) en waren er meerdere studies met een relatief kleine populatie en mede hierdoor een grote spreiding van de puntschatter van de uitkomstmaat (imprecision). Hierdoor werd de kwaliteit van dit bewijs naar beneden werd bijgesteld. Ook werden er veel verschillende doseringen ivermectine gebruikt en verschilde de duur van de behandeling.

De bewijskracht van de literatuur bij patiënten die waren opgenomen in het ziekenhuis en ambulante patiënten werd voor zowel de cruciale als belangrijke uitkomstmaten, door bovenstaande bevindingen gegradeerd als 'laag' of 'zeer laag'.

Ivermectine bij patiënten opgenomen in het ziekenhuis

Er werden 10 studies geïnccludeerd die ivermectine onderzochten bij patiënten die opgenomen waren in het ziekenhuis. Acht van de negen studies randomiseerden minder dan 100 patiënten naar ivermectine. Alleen de studie van Lim (2022) was groter: deze onderzocht bij 490 patiënten met minder dan 7 dagen klachten van COVID-19, een relatief hoge dosering ivermectine (400 microg/kg gedurende 5 dagen). De gerandomiseerde open-label trial was daarnaast van relatief goede kwaliteit. Er werd geen statistisch significant verschil gezien in de kans op progressie naar ernstige ziekte en ook een numeriek voordeel van ivermectine op deze uitkomst maat werd niet gezien (21,6% progressie naar ernstige ziekte in de ivermectine groep versus 17,3% in de controle groep). Voor de uitkomstmaat mortaliteit werd ook geen significant verschil gevonden, al was er hier wel een numeriek voordeel van ivermectine (1,2% mortaliteit binnen 28 dagen in de ivermectine groep versus 4,0% in de controlegroep).

Ook de andere RCT's die in deze richtlijn werden geïnccludeerd lieten geen overtuigend bewijs zien in het voordeel van ivermectine bij opgenomen patiënten. Ook als de data gepoold weergegeven werden (zoals

gedaan bij de mortaliteit binnen 28 dagen en bij start van uitgebreide respiratoire ondersteuning), werd er geen overtuigend bewijs gezien in het voordeel van ivermectine.

Ivermectine bij ambulante patiënten

Ook bij ambulante patiënten waren er een aantal kleine studies die minder dan 100 patiënten randomiseerden naar ivermectine. Twee grotere studies die het gebruik van ivermectine onderzochten in de ambulante setting, zijn de studie van López-Medina (2021) en Vallejos (2021). Verreweg het meeste bewijs naar ivermectine bij ambulante patiënten wordt verkregen uit de studie van Reis (2022) die 1358 patiënten includeerde.

López-Medina (2021) verrichtte een dubbelblinde, 1:1 gerandomiseerde, placebo-gecontroleerde, prospectieve studie bij 400 patiënten met milde ziekte in een vroege fase (minder dan 7 dagen klachten). De kwaliteit van deze studie is hoog met betrekking tot de opzet, uitvoering (inclusief blinding), analyse en documentatie. Ook de beperkingen zijn transparant benoemd. De gebruikte dosering en het doseringsschema van ivermectine is duidelijk hoger (300 microgram/kg gedurende 5 aaneengesloten dagen) dan de geregistreerde standaard dosis (200 microgram/kg eenmalig eventueel met een herhaling 1 week later). De mediane tijd tot verdwijnen van symptomen was 10 dagen (IQR 9 –13 d) met ivermectine versus 12 dagen (IQR 9 –13 d) met placebo, maar niet statistisch significant verschillend (HR: 1,07 [95% CI: 0,87 –1,32]; $P = 0,53$ met log-rank test). Op dag 21 waren 82% van de patiënten met ivermectine versus 79% met placebo symptoomvrij. Deze studie was niet gepowered om een effect op mortaliteit in de studiestudiepopulatie aan te tonen, die bij patiënten in deze leeftijdsgroep (mediaan 37 jaar) met milde COVID-19 hoe dan ook zeer laag is. Ook is er geen data over (het beloop) van *viral load* en bereikte ivermectine spiegels. In de ivermectine-groep werden niet meer bijwerkingen gerapporteerd dan in de placebogroep.

De studie van Vallejos (2021) onderzocht ivermectine bij ruim 500 patiënten met COVID-19. Net zoals de voorgaande studie, was ook deze studie van relatief goede kwaliteit en was de gebruikte dosering van ivermectine hoger dan de geregistreerde standaarddosis. Wel was de studie 'underpowered' omdat deze relatief klein was voor de gekozen uitkomstmaat (opname in het ziekenhuis). Patiënten waren relatief jong (42 jaar) en zij hadden nog maar kort klachten (gemiddeld 4 dagen bij randomisatie). Opname in het ziekenhuis was minder vaak nodig bij patiënten die ivermectine gebruikte (5,6% versus 8,4%), echter, dit verschil was niet statistisch significant. Ook werden er geen statistisch significante verschillen gevonden in de virale klaring, de kans op mechanische ventilatie of mortaliteit.

Een grote Braziliaanse, placebogecontroleerde RCT onderzocht ivermectine bij 1358 ambulante patiënten met COVID-19 (Reis, 2022). Deze zeer grote, kwalitatief goede studie includeerde patiënten met COVID-19 als ze maximaal 7 dagen klachten hadden van COVID-19 en minimaal 1 risicofactor voor progressie van ziekte. De mediane leeftijd van de gerandomiseerde patiënten was 49 jaar. Randomisatie bestond uit 400 microgram/kg ivermectine gedurende 3 dagen of placebo (gedurende 1, 3, 10 of 14 dagen). Er werd geen verschil gezien in de kans op opname in het ziekenhuis of bezoek aan de spoedeisende hulp vanwege COVID-19, in de groep met ivermectine versus placebo (14,7% in de ivermectine groep versus 16,3% in de placebo groep; relatief risico 0,90; 95% Bayesian CI 0,70-1,16). Ook werd er geen verschil gezien in mortaliteit of virale klaring.

Concluderend zijn er nu een drietal relatief grote en kwalitatief (redelijk) goede studies beschikbaar die het effect van ivermectine bij ambulante patiënten onderzochten. Geen van deze studies laat aanwijzingen zien voor een positief effect van ivermectine op de kans op opname in het ziekenhuis of mortaliteit.

Overige overwegingen

Studies bij zowel opgenomen als ambulante patiënten laten geen overtuigend positief effect zien van ivermectine op belangrijke klinische eindpunten. Dit betreft de mortaliteit, voorkomen van (ernstige) ziekte, voorkomen van opname op de intensive care, duur van ziekenhuisopname, en behoefte aan respiratoire ondersteuning.

Meerdere studies laten wel een verschil zien in de resolutie van symptomen in de groep die behandeld werd met ivermectine (bij opgenomen patiënten: *Ahmed, 2020; Lim, 2020; Mohan, 2021; Okumus 2021; Ravikirti, 2021; Shahbaznejad, 2021*; bij ambulante patiënten: *Buonfrate, 2022; Chachar, 2020; López-Medina, 2021; Podder, 2020*). Echter, deze klachten werden vaak alleen gedocumenteerd door middel van *self reporting*, hetgeen kans geeft op bias bij een niet geblindeerd studieontwerp. De relatief grote en kwalitatief betere studies van Lim (2022) en López-Medina (2021) lieten geen evident verschil zien in de resolutie van klachten. Ook onderzochten meerdere studies het effect van ivermectine op de *viral load*, met een wisselend resultaat. De studie van Ahmed (2021) toonde een significante reductie in de *viral load* na 3 dagen bij patiënten die met ivermectine behandeld werden, terwijl de studie van Chaccour (2021) en Vallejos (2021) dit niet bevestigen. Naast de bovengenoemde gepubliceerde artikelen zijn er diverse andere studies verschenen die niet gepeer-reviewed werden, of alleen verschenen in bronnen of tijdschriften die niet in de gebruikelijke online medische bibliografieën (bijvoorbeeld MEDLINE/Pubmed) zijn geïndexeerd. De richtlijncommissie heeft samen met het kennisinstituut van de FMS tevens een extra literatuuronderzoek gedaan naar de laatstgenoemde groep studies. Vele daarvan includeerden slechts kleine aantallen patiënten, lieten grote onduidelijkheid en/of gebreken zien wat betreft de gevolgde methodologie, of rapporteerden het resultaat op onduidelijke wijze.

Er zijn inmiddels wel- en niet gepeer-reviewde meta-analyses en reviews te vinden waarin onder andere de bovengenoemde studies ook werden opgenomen, en die dan op een positief advies uitkomen. De bron van deze meta-analyses is vaak onduidelijk, en deze meta-analyses bevatten aanzienlijke methodologische gebreken. Bijvoorbeeld: Bij het nalopen van deze meta-analyses bleek dat de waardering van het bewijsniveau van de afzonderlijke studies (volgens de GRADE-methodologie) niet goed was uitgevoerd, en dat ook studies en eindpunten werden meegenomen die (om diverse redenen) niet gepooled zouden mogen worden met de resultaten van andere studies (Hill, 2022) (heterogeniteit).

Bijwerkingen

Behandeling met ivermectine lijkt relatief veilig, al worden centraal zenuwstelsel bijwerkingen, zoals hoofdpijn en duizeligheid, maar ook encephalopathie, beschreven (Guzzo, 2002). 'Adverse events' tijdens behandeling van COVID-19 werden onder andere bekeken in de studie van Lim (2022) en López-Medina (2021). Bij Lim (2022) werden 'adverse events' gezien bij 13,7% van de patiënten die met ivermectine behandeld werden versus 4,4% van de patiënten in de controle groep. Dit verschil werd met name bepaald door het optreden van diarree. In de studie van López-Medina (2021) werden 'adverse events' niet vaker gezien in de ivermectine groep vergeleken met de placebo groep, wel stopte iets meer mensen in de ivermectine groep met hun behandeling vanwege klachten (7,5% versus 2,5%).

Dosering

In de beschreven studies worden veel verschillende doseringen van ivermectine gebruikt, daarnaast is de frequentie van toediening erg wisselend. Op basis van de huidige literatuur is behandeling met ivermectine niet geadviseerd. Ook zal er dus geen advies over een dosering plaatsvinden.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens wordt ivermectine niet aanbevolen in de behandeling van patiënten met COVID-19. Behandeling met ivermectine is relatief veilig, alhoewel er wel (ernstige) bijwerkingen zijn beschreven. Ondanks dit advies om ivermectine niet te gebruiken in de behandeling van COVID-19, verwachten wij dat patiënten bij hun waardering van ivermectine ook hun persoonlijke voorkeur en maatschappelijke beeldvorming zullen laten meewegen.

Kosten (middelenbeslag)

Ivermectine wordt niet aanbevolen bij de behandeling van COVID-19, de kosten zullen hier daarom niet beschreven worden.

Aanvaardbaarheid, haalbaarheid en implementatie

Ivermectine wordt niet aanbevolen bij de behandeling van COVID-19, dus implementatie is niet van toepassing.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De huidige literatuur bevat inmiddels zowel in de ambulante setting als bij opgenomen patiënten enkele relatief grote en kwalitatief (redelijk) goede studies die het effect van ivermectine bij COVID-19 onderzochten. Op basis van deze literatuur wordt er geen voordeel verwacht van ivermectine bij de behandeling van COVID-19. Op basis van de beschikbare *in vitro* en *in vivo* data is het ook twijfelachtig of van ivermectine een (relevant) antiviraal effect bij patiënten te verwachten is. Het (*off label*) gebruik van ivermectine in de behandeling van COVID-19 wordt dan ook niet aanbevolen.

Ook de richtlijnen van de WHO, de Infectious Diseases Society of America (IDSA) en de National Institute of Health (NIH) hebben ivermectine niet opgenomen als standaardbehandeling. De fabrikant Merck heeft op 4-2-2021 bevestigd dat ivermectine als niet geschikt wordt beschouwd voor de behandeling van COVID-19 (zie: www.merck.com/news/merck-statement-on-ivermectin-use-during-the-covid-19-pandemic)

Onderbouwing

Achtergrond

Ivermectine is een semisynthetisch derivaat van avermectine en wordt gebruikt voor de behandeling van parasitaire infestaties of infecties met mijten of nematoden bij dieren en mensen. Over ivermectine werd *in vitro* activiteit tegen SARS-CoV-2 bij een derivaat van Vero cellen (niercellen afkomstig van groene meerapen) gerapporteerd (Caly, 2020). Het mechanisme voor de anti-parasitaire werking is gebaseerd op verslapping van gladde spiercellen door remming van *Cl⁻ channels*, warentegen het mechanisme voor anti-virale werking zou kunnen berusten op de remming van *nuclear import* (Jans, 2020). Een latere studie met humane primaire bronchiaalepitheel cellen als model, dat beter overeenkomt met de situatie bij mensen, toonde echter geen remming van de virusreproductie *in vitro* (Dinesh Kumar, 2021). Dit maakt de extrapolatie naar klinische effecten niet eenvoudiger.

Klinische behandeling van COVID-19 met ivermectine werd in het begin van de pandemie ontraden omdat met een 10 keer hogere dan de geregistreerde dosis de *in vitro* EC₅₀ (die ook niet klinisch gevalideerd is), in de long niet bereikt zou kunnen worden. Alleen met een vele malen (>35-100x) hogere dosis dan de standaarddosis zouden theoretisch pas de benodigde concentraties ook *in vivo* bereikt kunnen worden (Schmith, 2020). Klinische dose-finding studies ontbreken.

Inmiddels hebben diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit van ivermectine onderzocht om de plaats van dit middel bij de behandeling van COVID-19 patiënten te bepalen.

Conclusies / Summary of Findings

PICO 1: Hospitalized patients

Mortality (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with ivermectin on mortality when compared with treatment without ivermectin in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2021; Gonzalez, 2022; Krolewiecki, 2020; Lim, 2022; Mohan, 2021; Okumuş 2021; Ravikirti, 2021</i>

Extensive respiratory support (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with ivermectin on extensive respiratory support when compared with treatment without ivermectin in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2021; Lim, 2022; Mohan, 2021; Ravikirti, 2021; Shahbaznejad, 2020</i>

Duration of hospitalization (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with ivermectin on the length of stay when compared with treatment without ivermectin in <u>hospitalized</u> patients with COVID-19. <i>Source: Abd-Elsalam, 2021; Ahmed, 2020; Gonzalez, 2022; Kishoria, 2020; Li, 2022; Mohan, 2021; Rivikirti, 2021; and Shahbaznejad, 2021</i>

Time to clinical improvement (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with ivermectin on time to clinical improvement when compared with treatment without ivermectin in <u>hospitalized</u> patients with COVID-19. <i>Source: Ahmed, 2020; Lim, 2020; Mohan, 2021; Okumuş 2021; Ravikirti, 2021; Shahbaznejad, 2021</i>

PICO 2: Non-hospitalized patients

Mortality (crucial)

Low GRADE	Treatment with ivermectin may result in little to no difference in mortality when compared with treatment without ivermectin in <u>non-hospitalized</u> patients with COVID-19. Source: Chaccour, 2021; López-Medina, 2021; Reis, 2022; Vallejos, 2021

Respiratory support (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with ivermectin on extensive respiratory support when compared with treatment without ivermectin in <u>non-hospitalized</u> patients with COVID-19. Source: López-Medina, 2021; Reis, 2022; Vallejos, 2021

Hospitalization (important)

Low GRADE	Treatment with ivermectin may result in little to no difference in hospitalization when compared with treatment without ivermectin in <u>non-hospitalized</u> patients with COVID-19. Source: Buonfrate, 2022; Reis, 2022; Vallejos, 2021

Time to clinical improvement (important)

Low GRADE	Treatment with ivermectin may result in little to no difference in time to clinical improvement when compared with treatment without ivermectin in <u>non-hospitalized</u> patients with COVID-19. Source: Buonfrate, 2022; Chaccour, 2021; Chachar, 2020; López-Medina, 2021; Podder, 2020; Reis, 2022

Samenvatting literatuur

Hospitalized patients

Abd-Elsalam (2021) described an open-label randomized controlled trial, which was conducted in 2 university hospitals in Egypt. They evaluated the efficacy and safety of ivermectin in patients hospitalized with mild to moderate COVID-19. Of 172 patients, 164 patients were included as they met the inclusion criteria and were willing to participate. These patients were randomized to receive ivermectin and standard care (n=82) or standard care alone (n=82). The mean (SD) age was 42.38 (16.02) years in the intervention group, compared with 39.38 (16.92) years in the control group. In the intervention group 37/82 (45.1%) were males, compared with 45/82 (54.9%) in the control group. Patients in the intervention group received a single dose of oral ivermectin tablets (12 mg) every day for 3 days. In addition, all patients continued to receive standard of care for 14 days, which included paracetamol, oxygen, fluids (according to the condition of the patient), empiric antibiotic, oseltamivir if needed (75 mg/12 h for 5 days), and invasive mechanical ventilation with

hydrocortisone for severe cases. The length of the follow-up was 1 month. The following relevant outcome measures were included: mortality, duration of hospitalization and extensive respiratory support. The primary outcome was all-cause mortality within 1 month. This occurred in 3/82 (3.7%) patients in the intervention group, compared with 4/82 (4.9%) patients in the control group. This resulted in a rate difference of -0.01 (95% CI -0.07 to 0.05).

Ahmed (2020) described a randomized, double-blind, placebo-controlled trial, which was conducted in 1 hospital in Bangladesh. They evaluated the efficacy and safety of ivermectin in patients hospitalized with mild COVID-19. Patients were randomized to receive ivermectin alone (N=24), ivermectin and doxycycline (N=24) or placebo (N=24). For the current literature summary, the group receiving ivermectin alone was included as the intervention group. The standard care was not described. The mean age and sex were only reported for the three groups combined. Patients had a mean age of 42 years and 54% was female. Patients in the intervention groups received oral ivermectin alone (12 mg once daily, for 5 days). The control group received a placebo, which was not further specified. The length of the follow-up was 2 weeks. The following relevant outcome measures were included: non-invasive respiratory support, duration of hospitalization, time to clinical improvement, time to viral clearance. The primary outcomes were time to viral clearance and time to clinical improvement (remission of fever and cough). At day 14, viral clearance occurred in 17/22 (77.3%) patients in the intervention group and 9/23 (39.1%) patients in the control group. This resulted in a rate difference of -0.38 (95% CI 0.12 to 0.65). Remission of fever ($\geq 37.5^{\circ}\text{C}$) within 7 days occurred in 17/17 (100%) patients in the intervention group and 16/19 (84.2%) patients in the control group (RD 0.16 (95% CI -0.03 to 0.34). Remission of cough within 7 days occurred in 7/18 (38.9%) patients in the intervention group and 9/15 (60%) patients in the control group (RD -0.21, 95% CI -0.55 to 0.12).

Gonzalez (2022) described a double-blind, placebo-controlled, randomized clinical trial, which was conducted in Mexico. They evaluated the efficacy and safety of ivermectin in hospitalized COVID-19 patients that did not have severe respiratory failure. Patients were randomized to receiving ivermectin and standard of care or a placebo and standard of care. Another study arm was included, in which patients received hydroxychloroquine. This information is not included in the current summary. The mean age of patients was 56 (SD 16.5) years in the intervention group and 53.8 (SD 16.9) years in the control group. Patients in the intervention and control group were 58.3% and 62.1% male, respectively. The intervention group received a single dose of 12 mg (weight < 80kg) or 18 mg (weight $\geq$ 80kg) of ivermectin. The control group received calcium citrate as a placebo, which was administered as 2 tablets every 12 h on the first day, followed by one tablet every 12 h for the following 4 days. As standard of care, all patients received pharmacological thromboprophylaxis with low molecular weight heparin or unfractionated heparin according to local and international guidelines. The length of the follow-up was 28 days. The following relevant outcome measures were included: mortality and duration of hospitalization. The primary outcomes were length of hospital stay (median, days) and the rate of respiratory deterioration or death. The median length of stay was 6 (IQR 4-11) days in the intervention group and 5 (IQR 4-7) days in the control group. The rate of respiratory deterioration or death was 8/36 (22.2%) in the intervention group, compared with 9/37 (24.3%) in the control group (RD -0.02; 95% CI -0.21 to 0.17).

Kishoria (2020) described an open-label randomized controlled trial, which was conducted in one hospital in

India. They evaluated the efficacy and safety of ivermectin in hospitalized patients. Patients were randomized to receiving ivermectin and standard of care or standard of care alone. The mean age of all patients was 38 years (SD not reported) and 23/32 (72%) patients were male. The intervention group received a single dose of 12 mg of ivermectin. Standard of care provided to both groups and included hydroxychloroquine, vitamin C, and paracetamol. The length of the follow-up was 6 days. The following relevant outcome measure was included: duration of hospitalization. The primary outcome was negative RT-PCR throat swab for SARS-CoV-2 after 48 hours. In the intervention group, 8/19 (42.2%) patients had a negative swab, compared to 6/13 (46%) patients in the control group (RD -0.04, 95% CI -0.39 to 0.31).

Krolewiecki (2020) described a proof-of-concept, pilot, multicenter, open-label, randomized, controlled trial, which was conducted in four hospitals in Argentina. They evaluated the efficacy and safety of ivermectin in hospitalized patients with COVID-19 not requiring intensive care. Patients were randomized to receiving ivermectin and standard of care or standard of care alone. The mean ($\pm$ SD) age in the intervention group was 42.3 years ($\pm$ 12.8) and 38.1 years ($\pm$ 11.7) in the control group. In the intervention group, 15/30 (50%) of the patients were male, compared with 10/15 (67%) of the patients in the control group. The intervention group received oral treatment with ivermectin at a single dose of 600 μ g/kg for 5 consecutive days. Standard of care was provided to both groups and included hospitalization, but was not further specified. The length of the follow-up was 30 days. The following relevant outcome measure was included: mortality. The primary outcome was the difference in SARS-CoV-2 viral load between baseline and day 5. At day 5, 6/20 (30%) patients in the intervention group and 1/12 (8.3%) patients in the control group had a viral load value below the limit of quantification of 10 copies/reaction (RD 0.22, 95% CI -0.04 to 0.47).

Lim (2022) described a multicenter, open-label randomized controlled trial, which was conducted at 20 public hospitals and a COVID-19 quarantine center in Malaysia. They evaluated the efficacy of ivermectin in preventing progression to severe disease among high-risk patients with COVID-19. Patients were randomized to receiving ivermectin and standard of care or standard of care alone. The mean ($\pm$ SD) age in the intervention group was 63.0 years ($\pm$ 8.9) and 62.0 years ($\pm$ 8.4) in the control group. In the intervention group, 111/241 (46.1%) of the patients were male, compared with 112/249 (45.0%) of the patients in the control group. The intervention group received oral ivermectin 400 μ g/kg body weight daily for 5 days. Standard of care was provided to both groups and consisted of symptomatic therapy and monitoring for signs of early deterioration based on clinical findings, laboratory test results, and chest imaging, but was not further specified. The length of the follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement and extensive respiratory support. The primary outcome was proportion of patients who progressed to severe COVID-19. Of the intervention group, 52/ 241 patients (21.6%) progressed to severe COVID-19, compared to 43/249 (17.3%) patients in the control group (RD 0.04, 95% CI -0.03 to 0.11).

Mohan (2021) described a single-center, pilot, double-blind, randomized, placebo-controlled trial, which was conducted at a cancer institute in India. They evaluated the efficacy and safety of ivermectin in adult patients with non-severe COVID-19. Patients were randomized to receiving ivermectin 12 mg, ivermectin 24 mg or placebo. The mean ($\pm$ SD) age in the ivermectin 12 mg group was 36.3 years ($\pm$ 10.54), 34.3 years ($\pm$ 10.45) in the ivermectin 24 mg group and 35.3 years ($\pm$ 10.52) in the control group. In the ivermectin 12 mg group, 35/40 (57.5%) of the patients were male, compared with 37/40 (92.5%) of the patients in the ivermectin 24 mg

group and 39/52 (86.7%) of the patients in the control group. The intervention groups received oral treatment with ivermectin at a single dose of 12 mg (200 µg/kg) or 24 mg (400 µg/kg). The length of the follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement and extensive respiratory support. The co-primary outcomes were the reduction of viral load (estimated from CT value) and conversion to negativity of nasopharyngeal/oropharyngeal RT-PCR on day 5 after the intervention. The decrease in viral load (mean log₁₀ viral copies/mL; ±SD) from baseline up to day 5 was 3.05 (±2.29) in the first intervention group (ivermectin 24mg), 3.04 (±2.05) in the second intervention group (ivermectin 12mg) and 3.08 (±1.98) in the control group. At day 5, the RT-PCR was negative for 33/80 (41.3%) patients in the intervention group and 14/45 (31.1%) patients in the control group (RD 0.10, 95% CI -0.07 to 0.27).

Okumuş (2021) described a multicenter, single-blind, quasi-randomized, controlled phase 3 trial, which was conducted at 4 tertiary referral hospitals in Turkey. They evaluated the efficacy and safety of ivermectin in adult severely ill COVID-19 patients with pneumonia. Patients were randomized to receiving ivermectin and standard of care or standard care alone. The intervention group received treatment with ivermectin at a dose of 200 µg/kg for 5 days. Six patients (16.7%) in the intervention group were excluded after randomisation because a SNP mutation in *MDR-1/ABCB1* gene and/or haplotypes and mutations of the *CYP3A4* gene were detected (mutations involved in ivermectin metabolism). The mean (±SD) age in the intervention group was 58.17 years (±11.52) and 66.23 years (±13.31) in the control group. In the intervention group, 21/30 (70.0%) of the patients were male, compared with 19/30 (63.3%) of the patients in the control group. The length of the follow-up was 10 days. The following relevant outcome measures were included: mortality and time to clinical improvement. The primary outcomes were the clinical responses and drug side effects obtained in patients on the 5th day. At the end of the five-day treatment period, the rate of clinical improvement was 46.7% (14/30) in the intervention group, compared with 36.7% (11/30) in the control group.

(Ravi)kirti (2021) described a single-center, pilot, double-blind, randomized, placebo-controlled trial, which was conducted at the All India Institute of Medical Sciences, which served as a COVID-19 dedicated tertiary healthcare facility. They evaluated the efficacy and safety of ivermectin in adult patients with mild to moderate COVID-19. Patients were randomized to receiving ivermectin 12 mg or placebo. The mean (±SD) age in the intervention group was 50.7 years (±12.7) and 54.2 years (±16.3) in the control group. In the intervention group, 40/55 (72.7%) of the patients were male, compared with 41/57 (71.9%) of the patients in the control group. The intervention group received oral treatment with ivermectin at a single dose of 12 mg for two consecutive days. The length of the follow-up was 10 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement and extensive respiratory support. The primary outcome was the was a negative RT PCR report on day 6. Negative RT-PCR was reported for 13/55 (24%) patients in the intervention group and 18/57 (32%) patients in the control group (RD -0.08, 95% CI -0.24 to 0.09).

Shahbasznejad (2021) described a double-blind, placebo-controlled randomized controlled trial, which was conducted in two referral tertiary hospitals in Mazandaran, Iran. They evaluated the efficacy and safety of ivermectin in patients with COVID-19. Patients were randomized to receive ivermectin or a placebo in addition to standard care. The study included both children and adults (inclusion criterium: age > 5 years). The mean (±SD) age was 47.63 (22.20) years in the intervention group and 45.18 (23.11) years in the control group. In

the intervention group, 18/35 (51.4%) of the patients were male, compared with 18/34 (52.9%) of the patients in the control group. The intervention group received a single weight-based dose of oral dose of 200 µg/kg. The length of follow-up was 7 days. The following relevant outcome measures were included: mortality, duration of hospitalization, time to clinical improvement and extensive respiratory support. The primary outcome was mean time ($\pm$ SD) to clinical improvement, which was on average 4.2 ($\pm$ 0.3) days in the intervention group and 5.2 ($\pm$ 0.3) days in the control group (MD -1.00, 95% CI -1.14 to -0.86).

Non-hospitalized patients

Buonfrate (2022) described a phase 2, dose-finding, randomized, double-blind, placebo-controlled trial, which was conducted in 4 centres (not hospitals) in the United States. They evaluated the efficacy and safety of 2 dosages of ivermectin in outpatients. Patients were randomized to receive ivermectin (two dosages; N=29, N=32) or placebo (control group; N=32). The median (range) age was 47.0 (31.0-62.0) and 44.5 (31.0-55.5) years in the intervention groups and 50.0 (26.0-57.0) years in the control group. An imbalance in the sex ratio was observed; 14/29 (48.3%) and 8/32 (25.0%) of the patients in the intervention groups were female, compared with 17/32 (53.1%) of the patients in the control group. The intervention groups received either ivermectin 600 µg/kg plus placebo for 5 days or ivermectin 1200 µg/kg for 5 days. The control group received a placebo which was identical in number, appearance and taste to the ivermectin tablets. The length of follow-up was 30 days. The following relevant outcome measure was included: time to clinical improvement. The primary outcomes were number of serious adverse drug reactions and change in viral load from baseline to day 7. In both groups, no serious adverse drug reactions occurred. The mean ($\pm$ SD) change in viral load was 2.5 log₁₀ ($\pm$ 2.2) in the first intervention group (ivermectin 600 µg/kg), 2.0 log₁₀ ($\pm$ 2.1) in the second intervention group (1200 µg/kg) and 2.9 log₁₀ ($\pm$ 1.6) in the control group.

Chaccour (2021) described a pilot, double-blind, placebo-controlled randomized controlled trial, which was conducted in a university hospital in Spain. They evaluated the efficacy and safety of ivermectin in outpatients. Patients were randomized to receive ivermectin or placebo. The median (IQR) age was 26 (19-36) years in the intervention group and 26 (21-44) years in the control group. In the intervention group, 7/12 (58%) of the patients were male, compared with 5/12 (43%) of the patients in the control group. The intervention group received a single oral, tailored dosage of ivermectin. According to their weight and using tablets of 3 mg, the individual dose ranged from 400 µg/kg to a maximum of 457 µg/kg. The control group received a placebo. No details were provided about the standard of care. The length of the follow-up was 28 days. The following relevant outcome measure was included: mortality. The primary outcome was the proportion of patients with detectable SARS-CoV-2 RNA by PCR from nasopharyngeal swabs at day 7. At day 7 post treatment, 12/12 (100%) patients had a positive PCR for gene N in both groups. For gene E, 11/12 (91%) in the ivermectin and 12/12 (100%) in the placebo group had a positive PCR.

Chachar (2020) described an open-label randomized controlled trial, which was conducted in one hospital in Pakistan. They evaluated the efficacy and safety of ivermectin in outpatients. Patients were randomized to receiving ivermectin or not receiving ivermectin. The mean ($\pm$ SD) age was 40.60 ($\pm$ 17) years in the intervention group and 43.08 ($\pm$ 14.8) years in the control group. In the intervention group, 7/25 (68%) of the patients were male, compared with 14/25 (56%) of the patients in the control group. The intervention group received 3 doses of 12 mg of ivermectin in the first 24 hours. The control group received symptomatic treatment only,

which was not further specified. The length of the follow-up was 7 days. The following relevant outcome measure was included: time to clinical improvement. The primary outcome was not specified and the other outcomes of interest for the current summary were not described in the study.

López-Medina (2021) described a double-blind, randomized, placebo-controlled trial, which was conducted at a single site in Colombia. They evaluated the efficacy and safety of ivermectin in adult patients with mild COVID-19 and symptoms for 7 days or fewer (at home or hospitalized). The majority (99%) of patients was not hospitalized at recruitment. Therefore, this study is included in the analysis of non-hospitalized COVID-19 patients (PICO 2). Patients were randomized to receiving ivermectin or placebo. The median (IQR) age in the intervention group was 37 years (29-47.7) and 37 years (28.7-49.2) in the control group. In the intervention group, 78/200 (39%) of the patients were male, compared with 89/198 (45%) of the patients in the control group. The intervention group received oral treatment with ivermectin at a single dose of 300 µg/kg for 5 days. The length of the follow-up was 21 days. The following relevant outcome measures were included: mortality and time to clinical improvement. The primary outcome was the time from randomization to complete resolution of symptoms within the 21-day follow-up period. In intervention group, the time to complete resolution symptom was median (IQR) 10 days (9-13), compared with 12 days (9-13) in the control group (absolute difference -2, 95% CI -4 to 2; HR 1.07, 95% CI 0.87 to 1.32).

Podder (2020) described a single-center, open-label, quasi-randomized, controlled trial, which was conducted at health complex in Bangladesh. They evaluated the efficacy and safety of ivermectin in adult outpatients with COVID-19. Patients were recruited from the outpatient clinic and randomized to receiving ivermectin and standard of care or standard care alone. The mean ($\pm$ SD) age in the intervention group was 38.41 years ($\pm$ 11.02) and 39.97 years ($\pm$ 13.24) in the control group. In the intervention group, 23/32 (71.9%) of the patients were male, compared with 21/30 (70.0%) of the patients in the control group. The intervention group received treatment with ivermectin at a single dose of 200 µg/kg. The length of follow-up was 10 days. The following relevant outcome measure was included: time to clinical improvement. The primary outcome was not defined.

Reis (2022) described a double-blind, randomized, placebo-controlled, adaptive platform trial (TOGETHER), which was conducted in 12 public health clinics in Brazil. They evaluated the efficacy and safety of ivermectin in non-hospitalized patients with COVID-19. Patients were randomized to receiving ivermectin and standard of care or a placebo and standard of care. The median age of patients was 49 (IQR 39-57) years in the intervention group and 49 (IQR 37-56) years in the control group. Patients in the intervention and control group were 43.6% and 39.9% male, respectively. The intervention group received ivermectin at a dose of 400 µg per kilogram of body weight for 3 days. The control group received a placebo for 1, 3, 10, or 14 days, comparable to the active-treatment groups in the trial. Standard of care was the care provided by health care professionals in Brazil at the time of the trial. The length of the follow-up was 28 days. The following relevant outcome measures were included: mortality, duration of hospitalization and time to symptom resolution.

The primary outcomes was a composite outcome, combining hospitalization due to COVID-19 or an emergency department visit due to clinical worsening of COVID-19 (defined as the participant remaining under observation for > 6 hours), both within 28 days after randomization. This outcome occurred in 100/679

(14.7%) of the patients in the intervention group and in 111/679 (16.3%) patients in the control group (reported RR 0.90, 95% CI 0.70 to 1.16; calculated RD -0.02, 95% CI -0.05 to 0.02).

Vallejos (2021) described a double-blind, placebo-controlled randomized controlled trial, which was conducted in the community in the province of Corrientes, Argentina. They evaluated the efficacy and safety of ivermectin in preventing hospitalizations in patients with COVID-19. Patients were randomized to receive ivermectin or a placebo in addition to standard of care. The mean ($\pm$ SD) age was 42.58 ($\pm$ 15.29) years in the intervention group and 42.40 ($\pm$ 15.75) years in the control group. In the intervention group, 139/250 (55.6%) of the patients were male, compared with 125/251 (49.8%) of the patients in the control group. The intervention group received a weight-based dose of oral ivermectin for two consecutive days. The length of the follow-up was 30 days. The following relevant outcome measures were included: mortality, extensive respiratory support and duration of hospitalization. The primary outcome was hospitalization, which was required for 14/250 (5.6%) patients in the intervention group and for 21/251 (8.4%) patients in the control group (RR 0.67, 95% CI 0.35 to 1.29; RD -0.03, 95% CI -0.07 to 0.02).

Table 1. Overview of RCTs comparing IL-1 inhibitors with standard care (or placebo) in hospitalized COVID-19 patients.

Author	Disease severity, based on need for respiratory support*	Sample size	Dosage
Registration nr.			
<i>Hospitalized patients</i>			
Abd-Elsalam 2021 NCT04403555	Unclear; included in mixed patient group as the authors described mild and moderate disease	I: N=82 C: N=82 Total: 164	Single dose of oral ivermectin tablets (12 mg) every day for 3 days
Ahmed 2020 Not registered	Mild; disease severity was not specified but the results indicate that none of the patients required oxygen.	I: N=23 II: N=23 C: N=23 Total: N=72	I: oral ivermectin alone (12 mg daily, for 5 days) II: oral ivermectin in combination with doxycycline (12 mg ivermectin single dose and 200 mg stat doxycycline day-1 followed by 100 mg 12 hourly for next 4 days)

Gonzalez (2022)	Moderate; Patients were excluded if they required high oxygen volumes (face mask > 10 L/ min), if they had predictors of a poor response to high-flow oxygen nasal prong therapy, or if they required mechanical ventilation [9]. In the absence of these exclusion criteria, patients were included regardless of other risk factors for poor prognosis.	I: N= 36 C: N=37 Total: N= 73	ivermectin, 12 mg or 18 mg, according to patient weight (12 mg in patients <80 kg, 18 mg ≥ 80 kg)
Kishoria 2020 Not registered	Mild; described as mild/asymptomatic; hospitalized without oxygen supplementation	I: N=19 C: N=16 Total: N=35	ivermectin 12 mg, single dose
Krolewiecki 2020 NCT04381884	Mild; Only 1 patient (intervention group) had oxygen saturation < 94 % at baseline; none of the patients required intensive care	I: N=30 C: N=15 Total: N=45	single oral dose of ivermectin 600 µg/kg for 5 consecutive days
Lim 2022 NCT04920942	Mild; Patients that required oxygen were excluded	I: 241 C: 249 Total: N=490	oral ivermectin, 400 µg/kg body weight daily for 5 consecutive days
Mohan 2021 CTRI/2020/06/026001	Mild; inclusion criteria 'nonsevere COVID-19, i.e., room air saturation (SpO ₂) >90%, and with no hypotension or requirement of mechanical ventilation'. Authors report that the baseline clinical severity by WHO ordinal scale was 3 (i.e., hospitalized, not requiring supplemental oxygen) in the majority (92%) of patients, and was 4 (i.e., hospitalized, requiring supplemental oxygen) in the remaining patients.	I1: N=49 I2: N=51 C: N=52 Total: N=152	single oral dose of ivermectin 12 mg (200 µg/kg) or 24 mg (400 µg/kg)

Okumuş 2021 NCT04646109	Severe; inclusion criteria: presence of tachypnea ≥ 30 /min, peripheral capillary oxygen saturation (SpO ₂) level $< 90\%$ in room air, Partial pressure of oxygen (PaO ₂)/FiO ₂ < 300 in oxygen receiving patient b. Presence of specific radiological finding for COVID-19 in lung tomography (bilateral lobular, peripherally located, diffuse patchy ground glass opacities) c. Mechanical ventilation requirement d. Acute organ dysfunction findings; patients with SOFA (sepsis-related organ failure assessment) score > 2	I: N=36 (N=30 included in final analysis due to exclusion of patients with genetic mutations) C: N=30 Total: N=66	ivermectin 200 µg/kg for 5 days (36-50 kg: 9 mg; 51-65 kg: 12 mg; 66-79 kg: 15 mg; > 80 kg: 200 µg/kg)
(Ravi)kirti 2021 CTRI/2020/08/027225)	Mixed: mild (76.4%) and moderate (23.6%) disease; the majority of the patients was classified as 'mild' according since there was no evidence of breathlessness or hypoxia (normal saturation). Moderate (23.6%) was classified as breathlessness and/or hypoxia (saturation 90-94% on room air), respiratory rate of 24 or more and no features of severe disease.	I: N=55 C: N=57 Total: N=115	Single oral dose of ivermectin 12 mg for 2 consecutive days
Shahbasznejad 2021 IRCT20111224008507N3	Mixed: mild to severe; 13 patients (37.1%) in the intervention group and 18 patients (52.9%) in the control group presented with severe disease (tachypnea (respiratory rate of ≥ 24 breaths/min), need for mechanical ventilation, need for supplemental oxygen, and oxygen saturation of $< 94\%$ in the ambient air)	I: N=35 C: N=34 Total: N=69	Single oral dose of ivermectin 200 µg/kg
<i>Non-hospitalized patients</i>			

Buonfrate 2022 NCT04438850	Mild; outpatient setting, participants not required oxygen supplementation (COVID severity score <3)	I: N=32 II: N=29 C: N=32 Total: N=93	I: single dose ivermectin 600 µg/kg plus placebo for 5 days II: single dose ivermectin 1200 µg/kg for 5 days
Chaccour 2021 NCT04390022	Mild; outpatient setting	I: N=12 C: N=12 Total: N=24	400 mcg/kg single oral dose or placebo; individual dose ranged from 400 µg/kg to a maximum of 457 µg/kg.
Chachar 2020 NCT04739410	Mild; outpatient setting	I: N=25 C: N=25 Total: N=50	ivermectin 12 mg, 3 doses within the first 24 hours
López-Medina 2021 NCT04405843	Mild; patients were at home or hospitalized but not receiving high-flow nasal oxygen or mechanical ventilation	I: N=200 C: N=198 Total: N=398	single oral dose of ivermectin 300 µg/kg for 5 days
Podder 2020 Not registered	Mild; outpatient setting, no report of supplemental oxygen	I: N=32 C: N=30 Total: N=62	single oral dose of ivermectin 200 µg/kg
Reis (2022)	Mild; outpatient setting, no report of supplemental oxygen	I: N=679 C: N=679 Total: N= 1358 (total study including other arms N=2157)	Ivermectin at a dose of 400 µg per kilogram of body weight for 3 days

Vallejos 2021 NCT04529525.	Mild; outpatient setting; participants were excluded if they were they required home oxygen or required hospitalization	I: N=250 C: N=251 Total: N=501	2 oral doses of 6mg for body weight at inclusion and after 24 h for body weight of <80 kg (total 24 mg), 3 tablets of 6 mg for 80-110 kg (total 36 mg), 4 tablets >110 kg (total 48 mg)

**Disease severity categories:*

- *mild disease (no supplemental oxygen);*
- *moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);*
- *severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS].*

N: Total sample size; I: Intervention; C: Control

Results

Ten studies included patients that were admitted to the hospital and seven RCTs studied ivermectine in an outpatient setting. One study (López-Medina, 2021) included both patients that were admitted to the hospital and outpatients. As the majority of included patients (99%) were outpatients, this study was included in the literature summary for outpatients (PICO 2). Outcomes were pooled, if possible.

PICO 1: Hospitalized patients

Mortality (crucial)

Five studies (Abd-Elsalam, 2021; Gonzalez, 2022; Krolewiecki, 2020; Lim, 2022; Mohan, 2021) reported the mortality at 28 to 30 days follow-up. Two studies (Okumuş 2021; Ravikirti, 2021) reported mortality at a different follow-up and three studies (Ahmed, 2020; Kishoria, 2020; Shahbaznejad, 2020) did not report mortality rates.

Mortality, 28-30 days

Both Krolewiecki (2020) and Mohan (2021) reported that none of the patients in both groups died and therefore no difference was found between the intervention and control group.

Abd-Elsalam (2021) reported mortality for 3/82 (3.7%) patients in the intervention group and 4/82 (4.9%) patients in the control group (RR 0.75, 95% CI 0.17 to 3.25; RD -0.01, 95% CI -0.07 to 0.05). This difference is not considered clinically relevant.

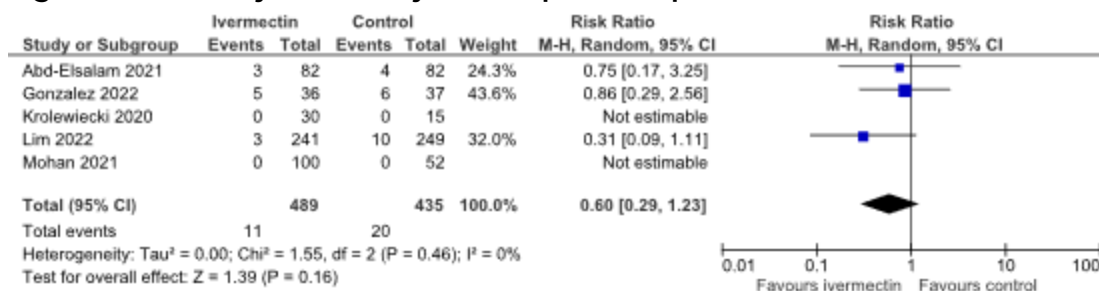
Gonzalez (2022) reported mortality for 5/36 (13.8%) patients in the intervention group and

6/37 (16.2%) patients in the control group (RR 0.86, 95% CI 0.29 to 2.56; RD -0.02, 95% CI -0.19 to 0.14). This difference is not considered clinically relevant.

Lim (2022) reported mortality for 3/241 (1.2%) patients in the intervention group and for 10/249 (4.0%) patients in the control group (RR 0.31, 95% CI 0.09 to 1.11; RD -0.03, 95% CI -0.06 to 0.00). This difference is considered clinically relevant.

The pooled incidence of mortality in hospitalized patients was 11/489 (2.2%) in the intervention group, compared to 20/435 (4.6%) in the control group. In two of the five studies, none of the patients died. The pooled relative risk (RR) was 0.60 (95% CI 0.29 to 1.23; Figure 1), and the risk difference (RD) was -0.01 (95% CI -0.03 to 0.00). This is not considered clinically relevant.

Figure 1: Mortality (28-30 days) in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Mortality, other follow-up

Ravikirti (2021) reported the mortality at a shorter follow-up of day 10. The incidence of mortality was 0/55 (0%) in the intervention group and 4/57 (7%) in the control group. This resulted in a RR of 0.12 (95% CI 0.01 to 2.09) and a RD of -0.07 (95% CI -0.14 to 0.00). This difference is considered clinically relevant.

Okumuş (2021) reported the mortality at a longer follow-up of 3 months. The incidence of mortality was 6/30 (20%) in the intervention group and 9/30 (30%) in the control group. This resulted in a RR of 0.67 (95% CI 0.27 to 1.64) and a RD of -0.10 (95% CI -0.32 to 0.12). This difference is considered clinically relevant.

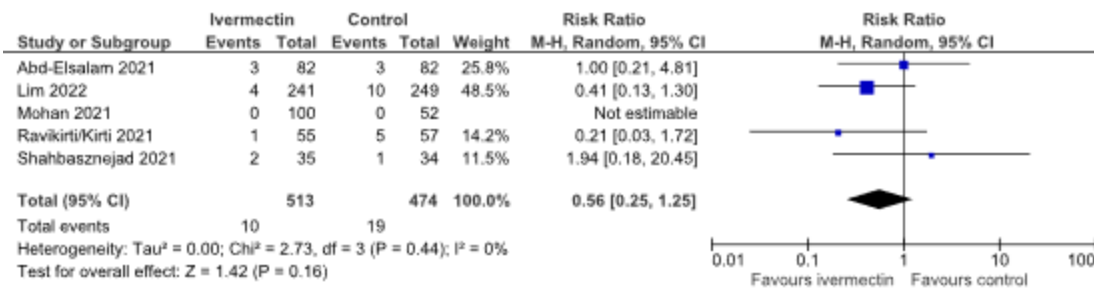
Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1), few events and wide CIs (imprecision, -2). Therefore, level of evidence for the outcome '*mortality*' is considered *very low*.

Extensive respiratory support (crucial)

Initiation of extensive respiratory support in hospitalized patients with COVID-19 was reported in five studies (Abd-El salam, 2021; Lim, 2022; Mohan, 2021; Ravikirti, 2021; Shahbaznejad, 2020). All five studies described the need or initiation of mechanical ventilation and did not further specify the ventilation method. Five studies did not report extensive respiratory support (Ahmed, 2020; Gonzalez, 2022; Kishoria, 2020; Krolewiecki, 2020; Okumuş, 2021).

Figure 2: Extensive respiratory support in hospitalized patients



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval

The pooled incidence of extensive respiratory support in hospitalized was 10/513 (1.9%) in the intervention group, compared to 19/474 (4.0%) in the control group. In one study (Mohan, 2021) none of the patients needed extensive respiratory support. The pooled RR was 0.56 (95% CI 0.25 to 1.25; Figure 1), and the RD was -0.01 (95% CI -0.03 to 0.01). This is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1), inconsistent findings (inconsistency, -1), few events, and wide CIs (imprecision, -1). Therefore, the level of evidence for the outcome '*extensive respiratory support*' is considered *very low*.

Duration of hospitalization (important)

Eight studies (Abd-El salam, 2021; Ahmed, 2020; Gonzalez, 2022; Kishoria, 2020; Li, 2022; Mohan, 2021; Rivikirti, 2021; and Shahbaznejad, 2021) reported the duration of hospitalization or the percentage of patients that was discharged at a specific follow-up. Two studies (Krolewiecki, 2020; Okumuş, 2021) did not report the duration of hospitalization.

Abd-El salam (2021), Ahmed (2020) Gonzalez (2022) and Shahbaznejad (2021) reported the length of hospital stay, whereas Lim (2022) reported the ICU stay. Abd-El salam (2021) reported that the mean duration of hospitalization was 8.82 (SD 4.94) days in the intervention group and 10.97 (SD 5.28) days in the control group (MD -2.15, 95% CI -3.72 to -0.58). Ahmed (2020) reported a mean duration of hospitalization of 9.6 (SD 4.39) days in the intervention group and 9.7 (SD 3.7) in the control group (MD -0.10, 95% CI -2.45 to 2.25). Gonzalez (2022) reported that the median length of stay was 6 (IQR 4-11) days in the intervention group and 5 (IQR 4-7) days in the control group. Shahbaznejad (2021) reported that the mean duration of hospitalization was 7.1 (SD 0.5) days in the intervention group and 8.4 (SD 0.6) days in the control group (MD -1.30, 95% CI -1.56 to -1.04). These differences are not considered clinically relevant.

In addition, Lim (2022) reported the duration of ICU stay. Patients in the intervention group stayed at the ICU for on average 7.7 (SD 4.4) days, compared to 7.3 days (SD 4.3) days in the control group (MD 0.40; 95% CI -0.36 to 1.16). This difference is not considered clinically relevant.

Kishoria (2020) reported the incidence of patients being discharged from the hospital at day 6. Of the intervention group, 8/19 (42.2%) patients were discharged, compared to 6/13 (46%) patients of the control group (RR 0.91, 95% CI 0.41 to 2.01; RD -0.04, 95% CI -0.39 to 0.31). This difference is not considered

clinically relevant.

Ravikirti (2021) reported the incidence of patients being discharged from the hospital at day 10. Of the intervention group, 44/55 (80%) patients were discharged, compared to 42/57 (74%) patients of the control group (RR 1.09, 95% CI 0.89 to 1.33; RD 0.06, 95% CI -0.09 to 0.22). Mohan (2021) reported the incidence of patients being discharged from the hospital at day 14. Of the intervention group, 75/80 (93.8%) patients were discharged, compared to 39/45 (86.7%) patients of the control group (RR 1.08, 95% CI 0.97 to 1.21; RD 0.07, 95% CI -0.02 to 0.16). These differences are considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1), inconsistent findings (inconsistency, -1) and low number of patients (imprecision, -1). Therefore, the level of evidence for the outcome '*duration of hospitalization*' is considered *very low*.

Time to clinical improvement (important)

Six studies (Ahmed, 2020; Lim, 2020; Mohan, 2021; Okumuş 2021; Ravikirti, 2021; Shahbaznejad, 2021) reported the time to clinical improvement or the incidence of clinical improvement at a specific follow up. Four studies (Abd-Elsalam, 2021; Gonzalez, 2022; Kishoria, 2020; Krolewiecki, 2020) did not report time to clinical improvement.

Mohan (2021) reported an average time to symptom resolution of 4.42 (SD 2.8) days in the intervention group and 4.58 (SD 2.94) days in the control group (MD -0.16, 95% CI -1.21 to 0.89). This difference is not considered clinically relevant.

Shahbaznejad (2021) defined clinical improvement as resolving a patient's baseline status on persistent and continuous cough (persistent cough for > 1 hour, or ≥ 3 coughing episodes in 24 hours, that interferes with activities of daily living and the ability to work) and tachypnea in addition to increasing oxygen saturation to > 94%. The mean time to clinical improvement was 4.2 (SD 0.3) days in the intervention group and 5.2 (SD 0.3) days in the control group (MD -1.00, 95% CI -1.14 to -0.86). This difference is not considered clinically relevant.

The other studies did not report the time to clinical improvement, but the incidence of resolution of symptoms within 5 to 7 days from the start of treatment.

Ahmed (2020) reported that remission of fever (≥ 37.5 °C) within 7 days occurred in 17/17 (100%) patients in the intervention group, compared to 16/19 (84.2%) patients in the control group (RD 0.16, 95% CI -0.03 to 0.34).

Lim (2022) reported that complete symptom resolution at day 5 occurred in 122/238 (51.3%) patients in the intervention group compared to 131/247 (53.0%) patients in the control group (RD -0.02, 95% CI -0.11 to 0.07).

Okumuş (2021) reported clinical improvement for clinical improvement at day 5 for 14/30 (46.7%) patients in the intervention group and 11/30 (36.7%) patients in the control group and for 22/30 (73.3%) and 16/30 (53.3%) patients at day 10 respectively (RD day 5: 0.10, 95% CI -0.15 to 0.35; RD day 10: 0.20, 95% CI -0.04 to 0.44).

Ravikirti (2021) reported that 46/55 (84%) patients in the intervention group and 51/57 (90%) patients in the control group were symptom free at day 6 (RD -0.06, 95% CI -0.18 to 0.07).

These differences are inconsistent, as they include both clinically relevant and irrelevant differences, in favour of the intervention group and control group.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1), and wide CIs (imprecision, -1) and inconsistent findings (inconsistency, -1). The level of evidence for the outcome '*time to clinical improvement*' is considered *very low*.

PICO 2: Non-hospitalized patients

Mortality (crucial)

Three studies (Chaccour, 2021; Reis, 2022; Vallejos, 2021) reported the 28 to 30 days mortality, one study reported mortality at a different follow-up (López-Medina, 2021) and three studies (Buonfrate, 2022; Chachar, 2020; Podder, 2020) did not report mortality.

Chaccour (2021) reported that none of the patients progressed to severe disease or death during the 28-day trial (RD mortality 0.00, 95% CI -0.15 to 0.15).

Reis (2022) reported mortality for 21/679 (3.1%) patients in the intervention group and 24/679 (3.5%) patients in the control group (RR 0.88, 95% CI 0.49 to 1.55; RD -0.00, 95% CI -0.02 to 0.01).

Vallejos (2021) reported all-cause mortality for 4/250 (1.6%) patients in the intervention group and 3/251 (1.2%) patients in the control group (RR 1.34, 95% CI 0.30 to 5.92; RD 0.00, 95% CI -0.02 to 0.02). Taken together, these studies reported mortality for 25/941 (2.7%) patients in the intervention group and 27/942 (2.9%) patients in the control group (RR 0.92, 95% CI 0.54 to 1.58; RD -0.00, 95% CI -0.01, 0.01). This is not considered a clinically relevant difference.

López-Medina (2021) reported mortality on day 21. The incidence of mortality was 0/200 (0%) in the intervention group and 1/198 (0.5%) in the control group. This resulted in a RR of 0.33 (95% CI 0.01 to 8.05) and a RD of 0.01 (95%CI -0.02 to 0.01). This is not considered a clinically relevant difference.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1), few events and wide CIs (imprecision, -2). Therefore, level of evidence for the outcome '*mortality*' is *low*.

Respiratory support (crucial)

Three studies (López-Medina, 2021; Reis, 2022; Vallejos, 2021) reported the need for respiratory support in non-hospitalized patients. The other four studies (Buonfrate 2022; Chaccour, 2021; Chachar 2020; Podder, 2020) did not reported the need for respiratory support in non-hospitalized patients.

López-Medina (2021) reported that 1 of the 200 (0.5%) patients in the intervention group needed respiratory support, compared to 1 of the 199 (0.5%) in the control group (RR 1.00; 95% CI 0.06 to 15.79). This is not considered a clinically relevant difference.

Reis (2022) reported that 19 of the 679 (2.8%) patients in the intervention group needed respiratory support, compared to 25 of the 679 (3.7%) patients in the control group (RR 0.77; 95% CI 0.43-1.36). This is not considered a clinically relevant difference.

Vallejos (2021) reported that 4 of the 250 (1.6%) patients in the intervention group needed respiratory support, compared to 3 of the 251 (1.2%) patients in the control group (OR 1.34; 95% CI 0.30 to 6.07). This is not considered a clinically relevant difference.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 3 levels, because of study limitations (risk of bias, -1), few events and wide CIs (imprecision, -2). Therefore, level of evidence for the outcome '*respiratory support*' is *very low*.

Hospitalization (important)

Three studies (Buonfrate 2022; Reis, 2022; Vallejos, 2021) reported the incidence of hospitalization. The other four studies (Chaccour, 2021; Chachar 2020; López-Medina, 2021; Podder, 2020) did not report the incidence of hospitalization.

Buonfrate (2022) reported that hospitalization was required for 4/59 (6.8%) patients in the combined intervention group and for 0/32 (0%) patients in the control group (RR 4.95, 95% CI 0.27 to 89.13; RD 0.07, 95% CI -0.01 to 0.15). This difference is considered clinically relevant.

Reis (2022) reported that hospitalization was required for 21/679 (3.1%) patients in the intervention group and for 24/679 (3.5%) patients in the control group (RR 0.83, 95% CI 0.63 to 1.10; RD -0.02, 95% CI -0.06 to 0.01). This difference is not considered clinically relevant.

Vallejos (2021) reported that hospitalization was required for 14/250 (5.6%) patients in the intervention group and for 21/251 (8.4%) patients in the control group (RR 0.67, 95% CI 0.35 to 1.29; RD -0.03, 95% CI -0.07 to 0.02). This difference is not considered clinically relevant.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1), low number of events (imprecision, -1). The level of evidence for the outcome '*hospitalization*' is considered *low*.

Time to clinical improvement (important)

Six studies (Buonfrate, 2022; Chaccour 2021; Chachar, 2020; López-Medina, 2021; Podder, 2020; Reis, 2022) reported the time to clinical improvement or the incidence of clinical improvement at a specific follow up. One study (Vallejos 2021) did not report time to clinical improvement.

Buonfrate (2022) reported the time to clinical improvement as the time from randomisation to clinical resolution, in which clinical resolution was not further specified. The median time to clinical resolution was 29 (IQR 13.5–32.0) days in the first intervention group (single dose ivermectin 600 µg/kg plus placebo for 5 days) and 14 (IQR 7–37) days in the second intervention group (single dose ivermectin 1200 µg/kg for 5 days) compared to 14 (IQR 13–30) days in the control group. The difference between the first intervention group receiving the low dose ivermectin and the control group is considered clinically relevant.

López-Medina (2021) reported that the median (IQR) time to resolution of symptoms was 10 (IQR 9-13) days for the intervention group and 12 (IQR 9-13) days for the control group. The reported absolute difference was -2 (95% CI -4 to 2) with an HR of 1.07 (95% CI 0.87 to 1.32). This difference is not considered clinically relevant.

Podder (2020) reported the time from the date of enrolment to symptom resolution. Time to symptom resolution was on average 5.31 (SD 2.48) days in the intervention group compared to 6.33 (SD 4.23) days in the control group. The MD was -1.02 (95% CI -2.76 to 0.72). This difference is not considered clinically relevant.

Reis (2022) reported the median (IQR) time to clinical recovery, which was assessed with the use of the World Health Organization clinical progression scale, but the threshold for 'recovery' was not further specified. Median recovery time was 14 (IQR 11-14) days in both the intervention and control group (HR 1.05 (0.88-1.24). This difference is not considered clinically relevant.

Chachar (2020) reported the incidence of patients being asymptomatic at day 7. In the intervention group, 16/25 (64%) patients were asymptomatic compared to 15/25 (60%) patients in the control group (RR 1.07, 95% CI 0.69 to 1.65; RD 0.04, 95% CI -0.23 to 0.31). This difference is not considered clinically relevant.

Chaccour (2021) reported the total number of patient-days that was self-reported by the treatment groups. Absolute data about the mean number of patient-days per patient, at which days these symptoms were reported or the hazard ratio were not available. Overall, the patients in the intervention group together reported fewer patient-days of any symptoms than those in the placebo group (symptoms reported for 171 vs 255 patient-days respectively). The authors report that this difference was mostly driven by the difference in anosmia/hyposmia (76 vs 158 patient-days) and cough (68 vs 97 patient-days). There were no major differences between the intervention and control group in the self-reported patient-days of fever (12 vs 12), general malaise (51 vs 61), headache (34 vs 38), or nasal congestion (91 vs 97). Only a small number of patient-days were reported for the experience of gastrointestinal symptoms (21 vs 6) and shortness of breath (3 vs 15).

Studies were not pooled, however, taken together the majority of studies did not find a clinically relevant difference between the intervention and control group.

Level of evidence of the literature

The level of evidence started as high, because the studies were RCTs. The level of evidence was downgraded by 2 levels, because of study limitations (risk of bias, -1) and wide CIs (imprecision, -1). The level of evidence for the outcome '*time to clinical improvement*' is considered *low*.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with ivermectin compared to treatment without ivermectin in patients with COVID-19?

PICO 1

- P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
- I: ivermectin + standard care
- C: standard care only / placebo treatment + standard care
- O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

- P: non-hospitalized with COVID-19 (subgroups mild, moderate, severe)
- I: ivermectin + standard care
- C: standard care only / placebo treatment + standard care
- O: 28-30 day mortality (if not available, other follow-up), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization and time to clinical improvement were considered as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS).

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and hospital admission (resulting in a NNT of 20).

Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until April 7th, 2022. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in indexed journal, comparing treatment with ivermectin and standard care to standard care alone or treatment with ivermectin and standard care to placebo and standard care in patients with COVID-19. Studies with $n < 10$ were excluded.

The systematic literature search resulted in 82133 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials. Eventually, 17 randomized controlled trials were included. Study inclusion was compared to studies included in a recent systematic review (Popp, 2021). In the current summary, two of these studies (Gonzalez, 2021; (Shah)Bukhari, 2021) were excluded because they were included as a preprint and not published in the meantime, and one study (Pott-Junior, 2021) was not included because of number of patients (<10 per arm). In addition, one individual study (Samaha, 2021) was first identified but was excluded as the publication was retracted by the journal.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, 17 studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Vitamine C

Uitgangsvraag

Wat is de plaats van vitamine C bij de behandeling van patiënten met COVID-19?

Aanbeveling

Gebruik vitamine C niet als behandeling van COVID-19

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder vitamine C. Tot en met 6 januari 2022 werden er 4 gerandomiseerde gecontroleerde studies (RCT's) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=163 in de interventiegroep en n=203 in de controlegroep) en 1 RCT bij patiënten buiten het ziekenhuis.

De geïnccludeerde studies onderzochten verschillende doseringen vitamine C, variërend van cumulatief 7 gram tot 168 gram in de eerste twee weken van de randomisatie. Ook werden verschillende toedieningsvormen gebruikt: intraveneus (JamaliMoghadamSiahkali, 2021; Kumari, 2020; Zhang, 2021) en oraal (Majidi, 2021; Thomas, 2021).

Er werden alleen randomiseerde trials geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat de studies steeds een relatief kleine populatie includeerden en omdat er mede hierdoor een grote spreiding van het betrouwbaarheidsinterval rondom de puntschatter van de uitkomstmaat was (imprecision), werd de kwaliteit van dit bewijs naar beneden bijgesteld. Daarnaast waren er drie open-label trials (JamaliMoghadamSiahkali, 2021; Kumari, 2020; Thomas, 2021), met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten. Ook om deze reden werd de kwaliteit van dit bewijs waar nodig naar beneden bijgesteld.

Vitamine C bij patiënten die waren opgenomen in het ziekenhuis

Op basis van de vier geïnccludeerde studies (JamaliMoghadamSiahkali, 2021; Kumari, 2020; Majidi, 2021 en Zhang, 2021) zijn we onzeker over het effect van behandeling met vitamine C op de cruciale uitkomstmaten mortaliteit en respiratoire ondersteuning. De studies zijn klein, met minder dan 100 patiënten per studie arm. De bewijskracht van de gevonden resultaten wordt daarnaast beperkt door tekortkomingen in de studieopzet. De bewijskracht is, bij beoordeling volgens de GRADE methodiek, 'zeer laag'. Er is dus sprake van een kennislacune.

Vitamine C bij ambulante patiënten

Op basis van één geïnccludeerde studie (Thomas, 2021) zijn we onzeker over het effect van behandeling met vitamine C op de cruciale uitkomstmaat mortaliteit bij ambulante patiënten met COVID-19. Ook in deze groep patiënten is de bewijskracht volgens de GRADE 'zeer laag'.

Ook de twee studies die initieel werden geëxcludeerd omdat ze een combinatie van vitamines gebruikten (Darban, 2021; Hakamifard, 2021) lieten in hun kleine populaties geen potentieel effect van vitamine C zien.

Overige overwegingen

Bijwerkingen

Vier van de geïnccludeerde studies rapporteerden ook 'adverse events'. Vanwege de kleine aantallen patiënten en de wisselende rapportage van eventuele bijwerkingen zijn er grote verschillen per studie te zien. In de studie van JamaliMoghadamSiahkali (2021) werden geen 'adverse events' gezien, terwijl in de studie van Thomas (2021) 17/43 (39.5%) van de patiënten in de interventiegroep een bijwerking ervaarde in de 7 dagen na de toediening van vitamine C ten opzichte van nul in de controlegroep. De volgende 'adverse events' werden gerapporteerd: hoofdpijn (n=1), misselijkheid (n=6), overgeven (n=1), tintelingen (n=1), pijn in epigastrio (n=5), diarree (n=7), duizeligheid/moeheid (n=1) en overig (n=1).

In bovenstaande studies leek het gebruik van vitamine C relatief veilig. Een RCT uit 2022 die vitamine C onderzocht bij meer dan 800 patiënten die met een sepsis op de intensive care lagen, toonde echter dat er mogelijk toch een nadeel was van vitamine C (Lamontagne, 2022). In deze studie werd een significant hogere mortaliteit of orgaan dysfunctie gezien bij patiënten die behandeld werden met vitamine C. In de subgroep van patiënten met sepsis door COVID-19 werd dit verschil niet gezien.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens wordt vitamine C niet aanbevolen als behandeling van COVID-19. Daarnaast laat een RCT bij patiënten met een sepsis zien dat behandeling met vitamine C mogelijk ernstige bijwerkingen kan hebben. Dit is niet op grote schaal onderzocht voor COVID-19. Ondanks het advies om vitamine C niet te gebruiken als behandeling van COVID-19, verwachten wij dat patiënten bij hun waardering van vitamine C ook hun persoonlijke voorkeur en maatschappelijke beeldvorming zullen laten meewegen.

Kosten (middelenbeslag)

Gezien het gebrek aan effectiviteit wordt vitamine C niet aanbevolen als behandeling van COVID-19.

Aanvaardbaarheid, haalbaarheid en implementatie

Vitamine C wordt niet aanbevolen als behandeling van COVID-19, dus de werkgroep voorziet geen problemen qua implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Op dit moment is er onvoldoende data om het gebruik van vitamine C aan of af te raden in de behandeling van COVID-19. Echter, gebruik van vitamine C zou gepaard kunnen gaan met (ernstige) bijwerkingen.

Onderbouwing

Achtergrond

Vitamine C is een antioxidant met anti-inflammatoire eigenschappen. Tijdens oxidatieve stress heeft het lichaam mogelijk meer vitamine C nodig, waardoor suppletie van vitamine C is geëvalueerd bij onder andere ernstige infecties en sepsis. In een onderzoeksmodel met muizen met een sepsis werd een langere overleving en minder inflammatie gezien in de groep die vitamine C kreeg toegediend (Fisher, 2011). Studies bij mensen

met een sepsis toonden tegenstrijdige resultaten. Een meta-analyse uit 2020 bij mensen met een sepsis toonde geen verbeterde mortaliteit binnen 28 dagen (Wei, 2020). Ook een gerandomiseerde klinische studie uit 2020 in kritisch zieke patiënten met een septische shock (n=211) toonde geen verschil aan tussen de combinatie van vitamine C (6000 mg/dag), thiamine (400 mg/dag) en hydrocortison (200 mg/dag) versus hydrocortison op de duur van de shock of op mortaliteit. Wel werd een verlaging van SOFA score gezien in de groep met de combinatie (mediane verandering van -2 punten vs -1 punt; P=0.02) (Fujii, 2020). Een studie in kritisch zieke patiënten met sepsis-geïnduceerde ARDS (n=167) toonde wel een lagere mortaliteit op dag 28 in de groep met 200 mg vitamine C/kg per dag (29.8% vs 46.3%; P=0.03). Echter, deze studie toonde geen verschil in SOFA score of inflammatoire markers (Fowler, 2019).

Inmiddels hebben diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit van vitamine C onderzocht om de plaats van dit middel bij de behandeling van COVID-19 patiënten te bepalen. Klinische dose-finding studies zijn in deze setting nooit verricht.

Conclusies / Summary of Findings

PICO 1: Treatment with vitamin C in hospitalized COVID-19 patients

Mortality (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on mortality when compared to treatment without vitamin C in <u>hospitalized</u> patients with moderate to severe COVID-19. <i>Sources: JamaliMoghadamSiahkali, 2021; Kumari, 2020 and Zhang, 2021</i>

Extensive respiratory support (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on extensive respiratory support when compared to treatment without vitamin C in <u>hospitalized</u> patients with moderate to severe COVID-19. <i>Sources: JamaliMoghadamSiahkali, 2021; Kumari, 2020 and Zhang, 2021</i>

Duration of hospitalization (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on length of stay when compared to treatment without vitamin C in <u>hospitalized</u> patients with moderate to severe COVID-19. <i>Sources: JamaliMoghadamSiahkali, 2021; Kumari, 2020 and Zhang, 2021</i>

Time to clinical improvement (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on time to clinical improvement when compared to treatment without vitamin C in <u>hospitalized</u> patients with moderate to severe COVID-19. <i>Source: Kumari, 2020</i>

PICO 2: Treatment with vitamin C in non-hospitalized COVID-19 patients

Mortality (crucial)

- GRADE	Due to low number of events, it is not possible to draw a conclusion on the effect of treatment with vitamin C on mortality when compared to treatment without vitamin C in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Thomas, 2021</i>

Hospitalization (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on hospitalization when compared to treatment without vitamin C in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Thomas, 2021</i>

Respiratory support (important)

- GRADE	No evidence was found regarding the effect of treatment with vitamin C on respiratory support when compared to treatment without vitamin C in <u>non-hospitalized</u> patients with COVID-19. <i>Source: -</i>

Time to clinical improvement (important)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin C on time to clinical improvement when compared to treatment without vitamin C in <u>non-hospitalized</u> patients with COVID-19. <i>Sources: Thomas, 2021</i>

Samenvatting literatuur

PICO 1: Treatment with vitamin C in hospitalized COVID-19 patients

JamaliMoghadamSiahkali (2021) described an open label randomized clinical trial, which was performed in

Iran. JamaliMoghadamSiahkali (2021) studied the efficacy and tolerability of vitamin C in adult hospitalized patients with moderate or severe COVID-19 disease. They included patients ≥ 18 years with a positive COVID-19 PCR test or COVID-19 suspicion based on clinical findings or imaging findings of COVID-19 on spiral/high-resolution CT imaging, clinical manifestations of ARDS or myocarditis and oxygen saturation $<93\%$ from admission or after 48 hours from the first COVID-19 treatment. Patients in the intervention group ($n=30$) received 1.5 g vitamin C (IV) every six hours for five days plus standard care. The control group ($n=30$) received standard care only. Standard care consisted of oral lopinavir (400mg)/ritonavir (100 mg) twice daily and a single dose of oral hydroxychloroquine (400 mg) on the first day of hospitalization. In case of deterioration during admission, patients received methylprednisolone (125 mg daily for three days). In the intervention group 26.6% of the patients received corticosteroids, compared to 23.3% of the patients in the control group. Vitamin C intake and/or levels at baseline were not reported. Patients were followed until discharge. Primary outcome measures included decrease in mortality and duration of hospitalization. In both groups, 3/30 (10%) patients died. In the intervention group, median (IQR) duration of hospitalization was 8.5 (7.0 tot 12.0) days, compared to 6.5 (4.0 to 12.0) days in the control group. Median length of stay at the ICU (IQR) was 5.5 (5.0 to 10.0) days in the intervention group, compared to 5.0 (5.0 to 7.0) days in the control group. Besides, the following relevant outcome measures were reported: respiratory support (intubation).

Kumari (2020) described an open label randomized clinical trial, which was performed in Pakistan. Kumari (2020) studied the efficacy of vitamin C in hospitalized patients with moderate to severe COVID-19. They included patients with severe COVID-19 based on the national health guidelines of Pakistan. Patients in the intervention group ($n=75$) received 50 mg/kg of vitamin C IV daily, plus standard care. The control group ($n=75$) received standard care only. Standard care was comparable between both groups and included antipyretics, dexamethasone (not mentioned in how many patients dexamethasone was used), and prophylactic antibiotics. Vitamin C intake and/or levels at baseline were not reported. Length of follow-up was not clear. Primary outcome was not specified. The following relevant outcome measures were reported: mortality, respiratory support (mechanical ventilation), duration of hospitalization and time to clinical improvement.

Majidi (2021) described a double-blinded controlled randomized clinical trial, which was performed in Iran. Majidi (2021) studied the efficacy and tolerability of vitamin C in adult patients with severe COVID-19 disease. They included patients between 35 and 75 years, who were positive for COVID-19, likely to be in the intensive care unit (ICU) for at least 48 hours and have an indication for enteral nutrition. Patients in the intervention group ($n=31$) received a 500 mg vitamin C capsule per day for 14 days, which was added to their enteral formula. The control group ($n=69$) received the same enteral nutrition, but without added vitamin C. There is no information available on usual care. Vitamin C intake and/or levels at baseline were not reported. Patients were followed for 14 days after start of the treatment. Survival at the ICU was determined 14 days after completion of the study. According to the study protocol, the primary outcome measures were several inflammatory and biochemical parameters. Results are described in Table 1. Beside the outcome measure survival, there was no other outcome measure of interest to our literature analysis.

Table 1. Primary outcome measures in Majidi (2021).

Outcome	Intervention group (post-intervention)*	Control group (post-intervention)*	Mean difference (95%CI)
White blood cells	11,828 ± 291	13,785 ± 378	-1957.00 (-2092.82 to -1821.18)
Neutrophils	8,660 ± 459	8,950 ± 238	-290.00 (-461.06 to -118.94)
Lymphocytes	1,175 ± 358	925 ± 427	250.00 (88.65 to 411.35)
Lactate dehydrogenase	Not reported	Not reported	N.A.
Creatine phosphokinase	Not reported	Not reported	N.A.
Cell blood count	For details, see Table 2 in Majidi (2021)	For details, see Table 2 in Majidi (2021)	
C reactive protein	Not reported	Not reported	N.A.
Partial pressure of oxygen	67.84 (± 23.02)	72.20 (± 8.21)	-4.36 (-12.69 to 3.97)
Partial pressure of carbon dioxide	44.35 (± 12.48)	40.70 (± 8.90)	3.65 (-1.22 to 8.52)

*Mean±SD

Zhang (2021) described a blinded placebo-controlled randomized clinical trial, which was performed in China. Zhang (2021) studied the efficacy and tolerability of vitamin C in adult patients with severe COVID-19 disease, admitted to the ICU. They included patients between 18 and 80 years, who were positive for SARS-CoV-2 infection confirmed by RT-PCR, had pneumonia confirmed by chest imaging, were admitted to the ICU and had P/F ratio < 300 mmHg. Patients in the intervention group (n=27) received 24 g vitamin C (IV) per day for seven days plus standard care. The control group (n=29) received placebo plus standard care. Standard care could include hydrocortisone 1 mg/kg/day, this was considered in case of rapid deterioration of hypoxemia, severe ARDS or septic shock. The study does not provide details on the number of patients with hydrocortisone. Vitamin C intake and/or levels at baseline were not reported. Patients were followed for 28 days after start of the treatment. The primary outcome measure was median invasive mechanical ventilation (IMV)-free days in 28 days. The intervention group had 26.0 (9.0 to 28.0) IMV-free days, compared to 22.0 (8.5 to 28.0) days in the control group. The Hazard Ratio (HR) (95%CI) was 4.8 (-4.7 to 7.2). The following relevant outcome measures were reported: 28-day mortality, duration of hospitalization, respiratory support (IMV, NIV and HFNC), improvement of the patient's condition.

Table 2. Overview of RCTs comparing vitamin C with standard care in hospitalized COVID-19 patients.

Author	Disease severity*	Sample size	Dosage
JamaliMoghadamSiahkali, 2021	Moderate to severe	I: 30 C: 30 Total: 60	1.5 g vitamin C intravenous every 6 h for 5 days
Kumari, 2020	Moderate to severe	I: 75 C: 75 Total: 150	50 mg/kg vitamin C intravenous every day (number of days unclear)
Majidi, 2021	Severe	I: 31 C: 69 Total: 100	500 mg vitamin C per os every day for 14 days
Zhang, 2021	Severe	I: 27 C: 29 Total: 56	24 g vitamin C intravenous every day for 7 days

*Disease severity categories:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

N: Total sample size

I: Intervention

C: Control

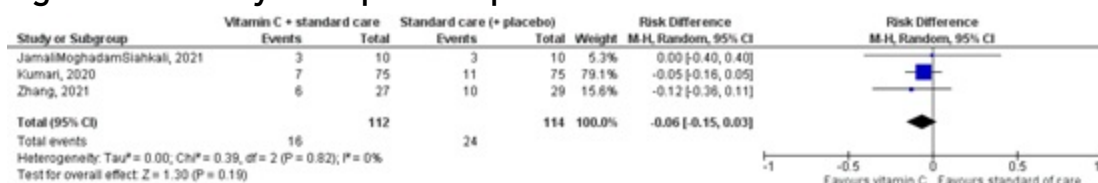
Results

Mortality (crucial)

JamaliMoghadamSiahkali (2021), Kumari (2020) and Zhang (2021) reported on the outcome measure mortality. Zhang (2021) reported on 28-day mortality and JamaliMoghadamSiahkali (2021) on in-hospital mortality. The follow-up period in the study of Kumari (2020) is not clear.

In total, 16/112 (14.3%) patients in the intervention groups died, compared to 24/114 (21.1%) patients in the control group (Figure 1). The risk ratio (RR) (95%CI) was 0.69 (0.39 to 1.22), in favour of the intervention group. The risk difference (RD) (95%CI) was -0.061 (-0.153 to 0.031), in favour of the intervention group. This difference is considered clinically relevant. Since Majidi (2021) only reported on 28-day survival at the ICU and data might be incomplete, it is not possible to incorporate the data of this study in the meta-analysis.

Figure 1: Mortality in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Subgroup patients with moderate and severe disease

JamaliMoghadamSiahkali (2021) and Kumari (2020) reported on the outcome measure mortality.

JamaliMoghadamSiahkali (2021) reported on in-hospital mortality. In the study of JamaliMoghadamSiahkali 3/30 (10.0%) patients died in both treatment groups. Patients were followed until discharge (no details provided). The follow-up period in the study of Kumari (2020) is not clear. In the intervention group in the study of Kumari (2020) 7/75 (9.3%) patients died, compared to 11/75 (14.7%) patients in the control group. The length of follow-up was not clear. The RR (95%CI) was 0.64 (0.26 to 1.55), in favour of the intervention group. The RD was -0.05 (-0.16 to 0.05), in favour of the intervention group. This difference is considered clinically relevant.

Subgroup patients with severe disease

Majidi (2021) reported on the outcome measure 28-day survival at the ICU. In the intervention group 16.1% patients survived, compared to 2.9% patients in the control group. It is not clear whether data on survival is complete. Therefore, it is not possible to conclude on the effect of treatment with vitamin C on the outcome measure mortality, based on the data of Majidi (2021).

Zhang (2021) reported on the outcome measure mortality after 28 days of follow-up. In the intervention group 6/27 (22.2%) patients died, compared to 10/29 (34.5%) patients in the control group. The HR (95%CI) was 0.5 (0.2 to 1.8), in favour of the intervention group. The RD (95%CI) was -0.12 (-0.36 to 0.11) in favour of the intervention group. This difference is considered clinically relevant (RD>3%).

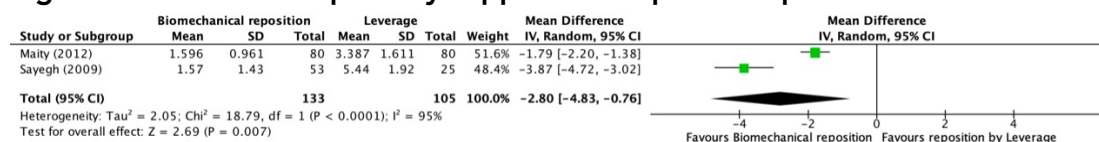
Level of evidence of the literature

The evidence for the outcome measure mortality comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (unclear randomization and/or allocation concealment, baseline differences and unclear follow-up, downgraded one level for risk of bias). Furthermore, the effect estimate (95%CI) crossed the thresholds for clinical relevance (downgraded two levels for imprecision).

Extensive respiratory support (crucial)

JamaliMoghadamSiahkali (2021), Kumari (2020) and Zhang (2021) reported on the outcome measure respiratory support and mechanical ventilation 'during admission' (JamaliMoghadamSiahkali, 2021 and Kumari, 2020), while Zhang reported this outcome 'after 7 days of treatment' (Zhang, 2021). In total, 27/128 (21.1%) patients in the intervention groups were intubated, compared to 30/128 (23.4%) patients in the control group (Figure 2). The RR (95%CI) was 0.90 (0.58 to 1.39), in favour of the intervention group. The RD (95%CI) was -0.02 (-0.12 to 0.08) in favour of the intervention group. This difference is not considered clinically relevant.

Figure 2: Extensive respiratory support in hospitalized patients



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Zhang (2021) also reported on the usage of High Flow Nasal Canula (HFNC), seven days after start of the treatment. They also reported on the number of days with mechanical ventilation (IMV) or HFNC during the 28 days of follow-up. In the intervention group 11/23 (47.8%) patients received HFNC at day seven, compared to 9/23 (39.1%) patients in the control group. The odds ratio (OR) (95%CI) was 1.4 (0.4 to 4.6), in favour of the control group. The RD (95%CI) was 0.09 (-0.20 to 0.37), in favour of the control group. This is considered clinically relevant (RD>5%). The median (IQR) number of days with HFNC was 0.5 (0.0 to 8.3) in the intervention group, compared to 2.0 (0.0 to 7.0) in the control group. The median (IQR) number of days with IMV was 1.5 (0.0 to 19.0) in the intervention group, compared to 6.0 (0.0 to 16.0) in the control group.

Level of evidence of the literature

The evidence for the outcome measure respiratory support comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (unclear randomization and/or allocation concealment, baseline differences, no or unclear blinding and risk of selective reporting, downgraded two levels for risk of bias). Furthermore, the effect estimate (95%CI) crossed the thresholds for clinical relevance (downgraded two levels for imprecision).

Duration of hospitalization (important)

JamaliMoghadamSiahkali (2021), Kumari (2020) and Zhang (2021) reported on the outcome measure duration of hospitalization. In the study of JamaliMoghadamSiahkali (2021) the median (IQR) duration of hospitalization was 8.5 (7.0 tot 12.0) days in the intervention group, compared to 6.5 (4.0 to 12.0) days in the control group. This difference in medians is not considered clinically relevant (less than three days).

In the study of Kumari (2020) mean ($\pm$ SD) duration of hospitalization in the intervention group was 8.1 ± 1.8 days, compared to 10.7 ± 2.2 days in the control group. The mean difference (95%CI) was -2.60 (-3.24 to -1.96) in favour of the intervention group. This is not considered clinically relevant (less than three days).

In the study of Zhang, mean ($\pm$ SD) duration of hospitalization in the intervention group was 35.0 ± 17.0 days, compared to 32.8 ± 17.0 days in the control group. The mean difference (95%CI) was 2.2 (-7.5 to 11.8) in favour of the control group. This is not considered clinically relevant (less than three days).

JamaliMoghadamSiahkali (2021) and Zhang (2021) also reported on the duration of ICU admission. In the study of JamaliMoghadamSiahkali (2021) median length of stay at the ICU (IQR) was 5.5 (5.0 to 10.0) days in the intervention group, compared to 5.0 (5.0 to 7.0) days in the control group. This difference in medians is not clinically relevant (<three days). In the study of Zhang (2021) mean ($\pm$ SD) length of stay at the ICU was 22.9 ± 14.8 days in the intervention group, compared to 17.8 ± 13.3 days in the control group. The mean difference (95%CI) was 5.0 (-2.5 to 12.7), in favour of the control group. This difference is considered clinically relevant (more than three days).

Level of evidence of the literature

The evidence for the outcome measure duration of hospitalization comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (no or unclear blinding, unclear randomization and allocation concealment, and baseline differences, downgraded two levels for risk of bias). Furthermore, the effect estimate (95% CI) crossed one of the thresholds for clinical relevance (downgraded one level for imprecision).

Time to clinical improvement (important)

Kumari (2020) reported on the outcome measure time to clinical improvement, which was not further defined. In the intervention group mean ($\pm$ SD) time to symptom resolution was 7.1 ± 1.8 days, compared to 9.6 ± 2.1 days in the control group. The mean difference (95%CI) was -2.5 (-3.13 to -1.87) in favour of the intervention group. This difference is not considered clinically relevant.

Level of evidence of the literature

The evidence for the outcome measure time to clinical improvement comes from a RCT and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (unclear allocation concealment and no blinding, downgraded two levels for risk of bias). Furthermore, the effect estimate (95% CI) crossed one of the thresholds for clinical relevance (downgraded one level for imprecision).

PICO 2: Treatment with vitamin C in non-hospitalized COVID-19 patients

Thomas (2021) described an open label randomized clinical trial, the COVID A to Z study. Thomas (2021) studied the efficacy and tolerability of ascorbic acid (vitamin C) in adult ambulatory patients with mild COVID-19 disease. They included adult patients who had a new diagnosis in an outpatient setting (timing between diagnosis and inclusion unclear). Patients in the intervention group ($n=48$) received 8000 mg of ascorbic acid, to be divided over two to three times per day with meals. The control group ($n=50$) received standard care, which was not further specified. Vitamin C intake and/or levels at baseline were not reported. Patients were followed for 28 days. The primary outcome measure was the number of days to 50% reduction in symptoms, including severity of fever, cough, shortness of breath, and fatigue. In the intervention group mean ($\pm$ SD) number of days until a 50% reduction in symptoms was 5.5 ± 3.7 days, compared to 6.7 ± 4.4 days in the control group. The following relevant outcome measures were reported: 28-day mortality, hospitalization, clinical improvement. Thomas (2021) did not report on the outcome measure respiratory support.

Table 3. Overview of RCTs comparing vitamin C with standard care in non-hospitalized COVID-19 patients.

Author	Sample size	Dosage
Thomas, 2021	I: 48 C: 50 Total: 98	8000 mg of ascorbic acid (divided over two to three times per day with meals), for 10 days.

Results

Mortality (crucial)

Thomas (2021) reported on the outcome measure 28-day mortality. In the intervention group, 1/48 (2.1%) died, compared to none of the 50 patients in the control group.

Level of evidence of the literature

Due to low number of events, it is not possible to draw a conclusion on the effect of treatment with vitamin C on mortality in non-hospitalized patients with COVID-19.

Respiratory support (important)

Thomas (2021) did not report on the outcome measures respiratory support. Therefore, it is not possible to conclude on the effect of treatment with vitamin C on respiratory support and viral clearance in non-hospitalized patients with COVID-19.

Level of evidence of the literature

-

Hospitalization (important)

Thomas (2021) reported on the outcome measure hospitalization. In the intervention group 2/48 (4.2%) patients were hospitalized, compared to 3/50 (6.0%) patients in the control group. The risk ratio (RR) (95%CI) was 0.69 (0.12 to 3.98), in favour of the intervention group. The risk difference (RD) (95%CI) was -0.02 (-0.11 to 0.07), in favour of the intervention group. This is not considered clinically relevant.

Level of evidence of the literature

The evidence for the outcome measure mortality comes from a RCT and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (open label study, differences in number of patients lost to follow-up and study was terminated earlier due to fulfillment of criteria for futility, downgraded two levels for risk of bias). Furthermore, the effect estimate (95%CI) crossed the thresholds for clinical relevance (downgraded two levels for imprecision).

Time to clinical improvement (important)

Thomas (2021) reported on the outcome measure number of days required to reach respectively a 50% reduction in symptom severity score from peak symptom score or a symptom severity score of zero. Symptom severity score was calculated based on a four symptom questionnaire (i.e. fever/chills, shortness of breath, cough and fatigue). From patients enrolled after July 16, 2020, symptom severity score was also calculated based on an expanded list of 12 symptoms (fevers/chills, shortness of breath, cough, fatigue, muscle or body aches, headache, new loss of taste, new loss of smell, congestion or runny nose, nausea, vomiting, and diarrhea). Data on the 12 symptoms severity score is only available for 33 patients and is therefore not included in our literature analysis.

Mean time ($\pm$ SD) to reach a four symptom severity score of zero was 12.1 ± 6.9 days in the intervention group, compared to 9.9 ± 4.4 days in the control group. The difference (95%CI) was 2.22 (-0.58 to 5.02) days, in favour of the control group. This is not considered clinically relevant (<three days). In the intervention group 46/48 (95.8%) patients reached a 50% reduction in the four symptom severity score, compared to 44/50 (88.0%) patients in the control group. Mean time ($\pm$ SD) to reach 50% reduction in the four symptom severity score was 5.5 ± 3.7 days in the intervention group, compared to 6.7 ± 4.4 day in the control group. The difference in days (95%CI) was 1.18 (-2.88 to 0.51), in favour of the intervention group. This is not considered clinically relevant.

Level of evidence of the literature

The evidence for the outcome measure time to clinical improvement comes from a RCT and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (open label study,

differences in number of patients lost to follow-up and study was terminated earlier due to fulfillment of criteria for futility, downgraded two levels for risk of bias). Furthermore, the effect estimate (95% CI) crossed one of the thresholds for clinical relevance (downgraded one level for imprecision).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectivity of treatment with vitamin C compared to standard treatment without vitamin C in patients with COVID-19?

PICO 1

P: hospitalized with COVID-19 (subgroups mild, moderate, severe)
I: vitamin C + standard care
C: standard care only / placebo treatment + standard care
O: 28-30 day mortality (if not available, any other reports of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

P: non-hospitalized patients with COVID-19
I: vitamin C + standard care
C: standard care only / placebo treatment + standard care
O: 28-30 day mortality (if not available, any other reports of mortality), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization and time to clinical improvement were considered as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS). Non-invasive respiratory support was defined as supplemental oxygen low flow oxygen or non-rebreathing mask.

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and hospital admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline

(preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until January 6th, 2022. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: randomized controlled trial, peer reviewed and published in indexed journal, comparing treatment with vitamin C and standard care to standard care alone or treatment with vitamin C and standard care to placebo and standard care in patients with COVID-19.

The systematic literature search resulted in 79974 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials (RCTs). Five RCTs were included (JamaliMoghadamSiahkali, 2021; Kumari, 2020; Majidi, 2021; Thomas, 2021 and Zhang, 2021). The studies of Darban (2021) and Hakamifard (2021) were not included, since they studied a combination of treatments, respectively a combination of vitamin C, melatonin and zinc (Darban, 2021) and of vitamin C and vitamin E (Hakamifard, 2021).

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

In total, five RCTs were included in the analysis of the literature. Four studies investigated the role of vitamin C in hospitalized patients (JamaliMoghadamSiahkali, 2021; Kumari, 2020; Majidi, 2021 and Zhang, 2021; submodule 1). One study investigated vitamin C in non-hospitalized patients (Thomas, 2021; submodule 2). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk-of-bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Vitamine D

Uitgangsvraag

Wat is de plaats van vitamine D bij de behandeling van patiënten met COVID-19?

Aanbeveling

Gebruik vitamine D niet als behandeling van COVID-19

Opmerking: voor aanbevelingen ten aanzien van het gebruik van vitamine D in de populatie wordt u verwezen naar het advies van de Gezondheidsraad

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen behandeling met en zonder vitamine D. Tot en met 30 september 2021 werden er 3 gerandomiseerde gecontroleerde studies (RCT's) gevonden in patiënten die waren opgenomen in het ziekenhuis (n=259 in de interventiegroep en n=243 in de controlegroep) en 1 RCT bij patiënten buiten het ziekenhuis.

De geïnccludeerde studies onderzochten verschillende preparaten van vitamine D: veelal gespecificeerd naar de specifieke vorm van vitamine D3 (genoemd vitamine D3 ofwel coledalciferol, calcifediol (vitamine D dat in de lever is omgezet in 25-hydroxyvitamine D) of calcitriol (het actieve 1,25-dihydroxycocledalciferol)). Daarnaast waren zowel de dosering als de frequentie van toediening variabel.

Er werden alleen randomiseerde trials geïnccludeerd in de analyse, waardoor de kwaliteit van bewijs initieel hoog was. Omdat de studies een relatief kleine populatie includeerden en omdat er mede hierdoor een grote spreiding van het betrouwbaarheidsinterval rondom de puntschatter van de uitkomstmaat was (imprecision), werd de kwaliteit van dit bewijs naar beneden bijgesteld. Daarnaast waren er twee open-label trials (Elamir, 2021; Enteras Castillo, 2020) met een mogelijk risico op vertekening van de studieresultaten (risk of bias) bij subjectieve uitkomstmaten. Ook om deze reden werd de kwaliteit van dit bewijs waar nodig naar beneden bijgesteld.

Vitamine D bij patiënten die waren opgenomen in het ziekenhuis

Op basis van de drie geïnccludeerde studies (Elamir, 2021; Enteras Castillo, 2020; Murai, 2021) zijn we onzeker over het effect van behandeling met vitamine D op de cruciale uitkomstmaat mortaliteit. De bewijskracht is, bij beoordeling volgens de GRADE methodiek, 'zeer laag'. Er is dus sprake van een kennislacune. Bij een gepoolde analyse van drie studies, werd er met zeer lage zekerheid een voordeel aangetoond van vitamine D (risico verschil -4% op de mortaliteit; 95% CI -13 tot 5%). Echter, de grootste en best uitgevoerde studie van Murai (2021) liet geen voordeel van vitamine D op de mortaliteit zien. Deze Braziliaanse studie liet ook geen verschil zien in opnameduur of de noodzaak tot mechanische ventilatie. Wel werd er een stijging van het serum vitamine D vastgesteld.

Vitamine D bij ambulante patiënten

Op basis van één geïnccludeerde Indiase studie (Rastogi, 2020) konden er geen conclusies getrokken worden

over het effect van vitamine D op de vooraf geformuleerde uitkomstmaten zoals mortaliteit, kans op opname in het ziekenhuis of extra zuurstofbehoefte of resolutie van klachten. Wel werd er gekeken naar de virale klaring. In deze studie werden opgenomen patiënten met milde of asymptomatische COVID-19 behandeld met colecalciferol wanneer de patiënten bij opname vitamine D deficiënt waren (25 [OH] vitamine D spiegel <20 ng/ml). Patiënten kregen dagelijks 60.000 IU colecalciferol of placebo. Op dag 21 waren meer patiënten in de colecalciferol-groep SARS-CoV2 negatief. Deze studie had echter kleine patiënten aantallen en patiënten met significante comorbiditeiten waren geëxcludeerd, waardoor de populatie zich niet goed laat vergelijken met de opgenomen populatie in Nederland.

Overig beschikbaar onderzoek

Over de rol van vitamine D bij COVID-19 zijn ook een groot aantal observationele studies gepubliceerd met forse methodologische beperkingen. Zo keken een drietal studies naar de relatie tussen 25 (OH) vitamine D spiegels en het risico op het krijgen van (een ernstig beloop van) COVID-19 (Abdollahi, 2020; De Smet, 2020; Luo, 2021). Hierbij werden patiënten met een (ernstige) COVID-19 retrospectief gematcht aan patiënten zonder COVID-19 of met een milder beloop. De spiegel van 25 (OH) vitamine D bleek statistisch significant lager bij patiënten met ernstige COVID, maar verschilde in alle genoemde studies in absolute zin minder dan 4 ng/ml tussen de verschillende groepen. De klinische relevantie van een dergelijk klein verschil is twijfelachtig. Daarnaast zijn de comorbiditeiten onvoldoende gerapporteerd in de studies, waardoor een vergelijking op basis van andere risicofactoren voor het krijgen van (ernstige) COVID niet te maken is. Of een lagere 25 (OH) vitamine D spiegel een verhoogd risico geeft op het krijgen van een ernstiger beloop van COVID-19 valt derhalve niet te zeggen.

In een groot genetisch cohortonderzoek (biobank van > 400.000 blanke Britse en > 40.000 Europese mensen) kon door middel van “Mendelian randomisation” geen associatie van (ernst van) COVID-19 met vitamine D spiegels en single-nucleotide polymorphisms (SNP’s) die geassocieerd zijn met lage vitamine D spiegels worden aangetoond (Butler-Laporte, 2021). Dit zou te verwachten zijn als er een invloed op de ziekte zou bestaan. Echter was de vrije fractie van vitamine D niet bekend in dit cohort en er is op basis van deze data ook geen uitspraak over een echte vitamine D deficiëntie mogelijk.

In maart 2021 sprak ook de Gezondheidsraad zich uit over de toevoeging van vitamine D aan de behandeling van COVID-19. Zij concludeerden dat er op dat moment te weinig bewijs was om een uitspraak te doen over een eventuele aanbeveling van extra vitamine D. Wel benadrukken zij dat een deel van de Nederlandse bevolking in aanmerking komt voor ‘reguliere’ suppletie van het vitamine D. Zie voor deze indicaties het rapport van de Gezondheidsraad uit 2008.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Op grond van de bekende onderzoeksgegevens wordt vitamine D niet aanbevolen als behandeling van COVID-19. Behandeling met vitamine D is wel relatief veilig, al zijn ernstige bijwerkingen als hypercalciëmie en hypercalciurie gemeld. Ondanks het advies om vitamine D niet te gebruiken als behandeling van COVID-19, verwachten wij dat patiënten bij hun waardering van vitamine D ook hun persoonlijke voorkeur en maatschappelijke beeldvorming zullen laten meewegen.

Kosten (middelenbeslag)

Gezien het gebrek aan effectiviteit wordt vitamine D niet aanbevolen als behandeling van COVID-19.

Aanvaardbaarheid, haalbaarheid en implementatie

Vitamine D wordt niet aanbevolen als behandeling van COVID-19, dus de werkgroep voorziet geen problemen qua implementatie.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Op dit moment zijn er onvoldoende data om het gebruik van vitamine D aan- of af te raden in de behandeling of preventie van patiënten met COVID-19.

Er blijft wel indicatie voor vitamine D suppletie met bekende doseringen buiten de indicatie van bescherming tegen COVID-19, zoals dit door de Gezondheidsraad wordt geadviseerd voor grote groepen in de bevolking.

Onderbouwing

Achtergrond

De vitamine D receptor komt tot expressie in immuuncellen, zoals B cel, T cel en antigeen-presenterende cellen, waardoor vitamine D de potentie heeft om de aangeboren en verworven immuniteit te moduleren (Aranow, 2011). In observationeel onderzoek is aangetoond dat vitamine D suppletie het aantal regulerende T cellen verhoogt en een verbeterde T cel activiteit geeft in gezonde vrijwilligers en mensen met auto-immuun ziektes (Fisher, 2019). Een lage vitamine D spiegel is geassocieerd met een hoger risico op een community-acquired pneumonie (CAP) bij zowel volwassenen als kinderen (Lu, 2017; Science, 2013). Ook een meta-analyse toonde dat vitamine D suppletie beschermt tegen het ontstaan van acute respiratoire infecties (Martineau, 2017). Echter, in twee gerandomiseerde, dubbelblinde, placebo-gecontroleerde onderzoeken leidde het toedienen van hoge dosis vitamine D aan zeer ernstig zieke patiënten met vitamine D deficiëntie niet tot een verkorting van de opnameduur of een verlaging van de mortaliteit ten opzichte van placebo (Amrein, 2014; Ginde, 2019). Daarnaast kunnen hoge spiegels van vitamine D leiden tot hypercalciëmie en nefrocalcinose (Del Valle, 2011).

Inmiddels hebben diverse gerandomiseerde gecontroleerde studies (RCT's) de effectiviteit van vitamine D onderzocht om de plaats van dit middel bij de behandeling van COVID-19 patiënten te bepalen. Klinische dose-finding studies zijn in deze setting nooit verricht.

Conclusies / Summary of Findings

Conclusions hospitalized COVID-19 patients

Mortality (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin D on mortality when compared with treatment without vitamin D in <u>hospitalized</u> patients with COVID-19. Sources: Entrenas Castillo, 2020; Murai, 2021 and Elamir, 2021

Extensive respiratory support (crucial)

Very low GRADE	The evidence is very uncertain about the effect of treatment with vitamin D on extensive respiratory support when compared with treatment without vitamin D in <u>hospitalized</u> patients with COVID-19. <i>Source: Murai, 2021 and Elamir, 2021</i>

Duration of hospitalization (important)

Low GRADE	Treatment with vitamin D may result in little to no difference in length of stay when compared with treatment without vitamin D in <u>hospitalized</u> patients with COVID-19. <i>Source: Murai, 2021 and Elamir, 2021</i>

Time to clinical improvement (important)

- GRADE	No evidence was found regarding the effect of treatment with vitamin D on time to clinical improvement when compared to treatment without vitamin D in <u>hospitalized</u> patients with COVID-19. <i>Source: -</i>

Treatment with vitamin D in non-hospitalized COVID-19 patients

Rastogi (2020) did not report on the crucial outcome measure mortality nor on the important outcome measures respiratory support, hospitalization and time to clinical improvement. Therefore, it is not possible to conclude on the effect of treatment with vitamin D on mortality, respiratory support, hospitalization and time clinical improvement in non-hospitalized patients with mild COVID-19 and vitamin D deficiency (<20 ng/ml).

- GRADE	No conclusions can be drawn about the effect of treatment with vitamin D, compared with treatment without vitamin D in <u>non-hospitalized</u> patients, because no studies were found that reported relevant outcomes for the comparison.

Samenvatting literatuur

Treatment with vitamin D in hospitalized COVID-19 patients

Elamir (2021) described an open-label, pilot randomized clinical trial, which was performed in Israel. Elamir (2021) studied the efficacy and safety of calcitriol supplementation in hospitalized patients with moderate COVID-19 disease. They included hospitalized adults with COVID-19 disease. Patients in the intervention group received a daily dose of 0.5 µg calcitriol for 14 days or until hospital discharge, plus standard of care. Patients in the control group received standard of care. Standard of care may include supplemental O₂, treatment with remdesivir (200 mg for one day followed by 100 mg for four days, 15% of the people in the

intervention group and 11% of the control group received remdesivir), dexamethasone (6 mg daily for ten days, 13% of the people in the intervention group and 12% in the control group received dexamethasone), or convalescent plasma (less than 5% in both groups). The primary outcome measure was SaO₂/FIO₂. In the intervention group the average ($\pm$ SD) increase in SaO₂/FIO₂ was 91.04 ± 119.08 , compared to an increase of 13.2 ± 127.7 in the control group. No postintervention scores were reported. Besides, the following relevant outcome measures were reported: mortality, extensive respiratory support, duration of hospitalization.

Entrenas Castillo (2020) described an open-label, double-masked pilot randomized clinical trial, which was performed in Spain. This was a pilot study prior to carrying out the **COVIDIOL-trial**. Entrenas Castillo (2020) studied the efficacy of vitamin D supplementation in hospitalized patients with moderate or severe COVID-19 disease. They included non-pregnant patients ≥ 18 years with COVID-19 clinical picture of acute respiratory infection, confirmed by radiographic pattern of viral pneumonia and a positive COVID-19 PCR test with CURB-65 severity scale. Patients in the intervention group (n=50) received calcifediol (0.532 mg on day 0 and 0.266 mg on day 3, day 7 and then weekly), plus standard of care. Patients in the control group (n=26) received standard of care. Standard of care consisted of hydroxychloroquine (400 mg every 12 h on day 1, 200 mg every 12 h for day 2-6), azithromycin (500 mg orally for 5 days) and for patients with pneumonia and NEWS score ≥ 5 , a broad spectrum antibiotic was added. Patients were followed until hospital discharge or death. The primary outcome measures were admission to the intensive care unit (ICU) and mortality. In the intervention group 0/50 patients died, compared to 2/26 (7.7%) patients in the control group. The risk difference (RD) (95%CI) was -0.08 (-0.19 to 0.04), in favour of the intervention group. In the intervention group 1/50 (2.0%) patient was referred to the ICU, compared to 13/26 (50.0%) patients in the control group. The RD (95%CI) was -0.48 (-0.68 to -0.28), in favour of the intervention group. No other relevant outcome measures were reported.

Murai (2021) described an multi-center, double-blind, placebo-controlled randomized clinical trial, which was performed in Brazil. Murai (2021) studied the efficacy and safety of vitamin D supplementation in hospitalized patients with moderate or severe COVID-19 disease. They included patients ≥ 18 years with a positive COVID-19 PCR test or CT scan findings compatible with the disease and diagnosis of flu syndrome with institutional criteria for hospitalization on hospital admission (respiratory rate > 24 /min, saturation $< 93\%$ or risk factors for complications). Patients in the intervention group (n=119) received an oral dose of 200.000 IU of vitamin D, plus standard of care. The control group (n=188) received placebo, on top of standard of care. Standard of care was not further described. Patients were followed until hospital discharge. The primary outcome was duration of hospitalization. In the intervention group the median (IQR) duration of hospitalization was 7 (4 to 10) days, compared to 7 (5 to 13) days in the control group. Besides, the following relevant outcome measures were reported: mortality (in-hospital), respiratory support.

Table 1. Overview of RCTs comparing vitamin D with standard of care in hospitalized COVID-19 patients.

Author	Disease severity	Vitamin D level at inclusion	Sample size	Dosage
Elamir, 2021	Moderate	No criteria	I: 25 C: 25 Total: 50	Daily dose of 0.5 µg calcitriol for 14 days or until discharge.
Entrenas Castillo, 2020	Moderate to severe	No criteria	I: 50 C: 26 Total: 76	Dose of 0.532 mg calcifediol on day 0 and of 0.266 mg on day 3 and 7, and then weekly until discharge or ICU admission.
Murai, 2021	Moderate to severe	No criteria	I: 119 C: 118 Total: 237	Single dose of 200000 IU vitamin D3

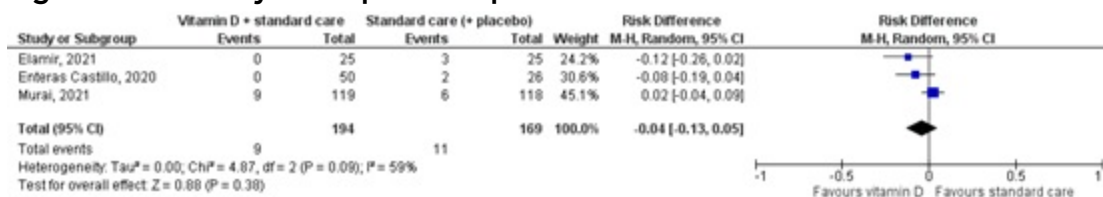
Results

Elamir (2021), Entrenas Castillo (2020) and Murai (2021) did not report on the important outcome measure time to clinical improvement.

Mortality (crucial)

Elamir (2021), Entrenas Castillo (2020) and Murai (2021), reported on the outcome measure mortality. Murai (2021) and Entrenas Castillo (2020) reported on mortality until hospital discharge. Elamir (2021) did not report on the follow-up period. In total, 9/194 (4.6%) patients in the intervention groups died, compared to 11/169 (6.5%) patients in the control group (Figure 1). The risk difference (RD) (95%CI) was -0.04 (-0.13 to 0.05), in favour of the intervention group. This difference is considered clinically relevant.

Figure 1: Mortality in hospitalized patients



Z: p-value of overall effect; **df:** degrees of freedom; **I²:** statistical heterogeneity; **CI:** confidence interval

Because of study heterogeneity and small sample sizes, we do not report mortality stratified according to disease severity.

Level of evidence of the literature

The evidence for the outcome measure mortality comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to very low. There was risk of bias (unclear allocation concealment, baseline differences and selective reporting of results, downgraded one level for risk of bias). Furthermore, the effect estimate (95%CI) crossed the thresholds for clinical relevance (downgraded two levels for imprecision).

Extensive respiratory support (crucial)

Elamir (2021) and Murai (2021) reported on the outcome measure extensive respiratory support. In the intervention group of Elamir (2021) none of the 25 patients was intubated, compared to 2/25 (8.0%) patients in the control group. In the intervention group of Murai (2021), 9/119 (7.6%) patients needed invasive mechanical ventilation (IMV), compared to 17/118 (14.4%) patients in the control group. The RR (95%CI) was 0.52 (0.24 to 1.13), in favour of the intervention group. The RD (95%CI) was -0.07 (-0.15 to 0.01), in favour of the intervention group. This is considered clinically relevant (RD>5%). Murai (2021) reported also on the duration of the respiratory support. Mean duration of IMV was 15.0 days in the intervention group, compared to 12.8 days in the control group (SD not reported). The mean difference (95%CI) is 2.2 (-8.4 to 12.8) days, in favor of the control group.

Level of evidence of the literature

The evidence for the outcome measure extensive respiratory support comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to low. There was risk of bias in one of the studies (unclear allocation concealment, baseline differences, open label study and unclear follow-up, downgraded one level for risk of bias). Furthermore, the effect estimate (95%CI) crossed one of the thresholds for clinical relevance and only two studies were included (downgraded two levels for imprecision).

Duration of hospitalization (important)

Elamir (2021) and Murai (2021) reported on the outcome measure duration of hospitalization. In the intervention group of Elamir (2021) the mean ($\pm$ SD) length of stay was 5.5 ± 3.9 days, compared to 9.2 ± 9.4 days in the control group. The mean difference (95%CI) was -3.7 (-7.7 to 0.3), in favor of the intervention group. This difference is considered clinically relevant (>three days). In the intervention group of Murai (2021) the median (IQR) duration of hospitalization was 7 (4 to 10) days, compared to 7 (5 to 13) days in the control group. This difference in medians is not considered clinically relevant (<three days).

Level of evidence of the literature

The evidence for the outcome measure duration of hospitalization comes from RCTs and therefore started at high certainty. The level of evidence was downgraded to low. There was risk of bias in one study (unclear allocation concealment, baseline differences, open label study and unclear follow-up, downgraded one level for risk of bias). The effect estimate (95%CI) crossed one of the thresholds for clinical relevance and only two studies were included (downgraded one level for imprecision).

Time to clinical improvement (important)

Elamir (2021), Entrenas Castillo (2020) and Murai (2021) did not report on the important outcome measure time to clinical improvement. Therefore, it is not possible to conclude on the effect of treatment with vitamin D on time to clinical improvement in hospitalized patients with moderate to severe COVID-19.

Level of evidence of the literature

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Treatment with vitamin D in non-hospitalized COVID-19 patients

Summary of literature

Description of studies

Rastogi (2020) described a placebo-controlled randomized clinical trial (**SHADE-study**), which was performed in India. Rastogi (2020) studied the efficacy and safety of cholecalciferol supplementation in patients with mild COVID-19 and vitamin D deficiency. They included patients with mildly symptomatic or asymptomatic COVID-19, 25 (OH)D level <20 ng/ml and with/without comorbidities. Median baseline 25 (OH)D levels were 8.36 (IQR 7.1 to 13.1) in the intervention group versus 9.5 (IQR 8.1 to 12.5) in the control group. Patients who were unable to take oral supplementation were excluded (e.g., invasive ventilation or severe comorbidities). Patients in the intervention group (n=16) received 60000 IU daily of cholecalciferol for 7 days plus standard of care, in order to achieve 25 (OH)D level >50 ng/ml. When 25 (OH)D levels >50 ng/ml at day 7, patients received weekly supplementation of 60.000IU. In case of lower 25 (OH)D levels, daily supplementation of 60.000 IU was continued. Patients in the control group (n=24) received placebo (distilled water) and standard of care (per institute protocol). Patients were followed until day 21 or virus negativity. The primary outcome measure was the proportion of participants being SARS-CoV-2 negative before the third week. In the intervention group, 10/16 (62.5%) patients were SARS-CoV-2 negative before the third week, compared to 5/24 (20.8%) patients in the control group. The Risk Difference (RD) (95%CI) was 0.42 (0.13 to 0.70), in favour of the intervention group. No other relevant outcome measures were reported.

Table 3. Overview of RCTs comparing vitamin D with standard of care in non-hospitalized COVID-19 patients

Author	Vitamin D level at inclusion	Sample size	Dosage
Rastogi, 2020	<20 ng/ml	I: 16 C: 24 Total: 40	Daily dose of 60000 IU cholecalciferol for 7 days - 25 (OH)D levels >50 ng/ml at day 7 à weekly supplementation of 60000IU - 25 (OH)D levels <50 ng/ml à daily supplementation of 60000 IU

Results

Rastogi (2020) did not report on the crucial outcome measure mortality nor on the important outcome measures respiratory support, hospitalization and time to clinical improvement.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What is the effectivity of treatment with vitamin D compared to standard treatment without vitamin D in patients with COVID-19?

PICO 1

P: hospitalized patients with COVID-19 (subgroups mild, moderate, severe)

- I: vitamin D + standard care
 C: standard care only / placebo treatment + standard care
 O: 28-30 day mortality (if not available, any other report of mortality), extensive respiratory support, duration of hospitalization, time to clinical improvement

PICO 2

- P: non-hospitalized patients with COVID-19
 I: vitamin D + standard care
 C: standard care only / placebo treatment + standard care
 O: 28-30 day mortality (if not available, any other report of mortality), respiratory support, hospitalization, time to clinical improvement

Relevant outcome measures

PICO 1: For hospitalized COVID-19 patients, mortality and need for extensive respiratory support were considered as crucial outcome measures for decision making. Duration of hospitalization and time to clinical improvement were considered as important outcome measures for decision making.

PICO 2: For non-hospitalized COVID-19 patients, mortality was considered as a critical outcome measure for decision making. Hospitalization, respiratory support and time to clinical improvement were considered as important outcome measures for decision making.

Extensive respiratory support was defined as high flow nasal cannula (HFNC)/Optiflow, continuous positive airway pressure (CPAP), non-invasive ventilation (NIV), mechanical ventilation or extracorporeal membrane oxygenation (ECMO or ECLS). Non-invasive respiratory support was defined as supplemental oxygen low flow oxygen or non-rebreathing mask.

The working group defined 3% points absolute difference as a minimal clinically important difference for mortality (resulting in a NNT of 33), 3 days for duration of hospitalization and time to clinical improvement, 5% points absolute difference need for respiratory support and hospital admission (resulting in a NNT of 20).

The results of studies in non-hospitalized and hospitalized patients are summarized separately. Studies of hospitalized patients were categorized based on the respiratory support that was needed at baseline (preferably based on patient inclusion/exclusion criteria; otherwise on baseline characteristics). The following categories were used:

- mild disease (no supplemental oxygen);
- moderate disease (supplemental oxygen: low flow oxygen, non-rebreathing mask);
- severe disease (supplemental oxygen: high flow oxygen [high flow nasal cannula (HFNC)/Optiflow], continuous positive airway pressure [CPAP], non-invasive ventilation [NIV], mechanical ventilation, extracorporeal membrane oxygenation [ECMO or ECLS]).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms

until September 30th, 2021. The detailed search strategy is outlined under the tab Methods. Studies were selected based on the following criteria: (systematic review of) randomized controlled trial(s), peer reviewed and published in indexed journal, comparing treatment with vitamin D and standard of care to standard of care alone or treatment with vitamin D and standard of care to placebo and standard of care in patients with COVID-19.

The systematic literature search resulted in 77680 hits. Studies were selected based on the following criteria: systematic review or randomized controlled trials (RCTs). One systematic review (Stroehlein, 2021) and four RCTs (Murai, 2021; Castillo, 2020; Elamir, 2021 and Rastogi, 2021) fulfilled the inclusion criteria. Since Stroehlein (2021) only included Murai (2021), Castillo (2020) and Rastogi (2021), we decided not to use this systematic review in the literature analysis. Additionally, published articles that were subsequently retracted were not included.

Statistical methods

Statistical analyses were conducted using Review Manager (RevMan) software 5.4. For dichotomous outcomes, Mantel Haenszel random-effects risk ratios (RRs) and risk differences (RDs) were calculated. For continuous outcomes, a random-effects mean difference (MD) weighted by the inverse variance was calculated. The random-effects model estimates the mean of a distribution of effects.

Results

Four RCTs were included in the analysis of the literature (Murai, 2021; Castillo, 2020; Elamir, 2021 and Rastogi, 2021). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 03-10-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Startpagina - Tromboseprofylaxe bij COVID-19

Waar gaat deze richtlijnmodule over?

Deze richtlijnmodule geeft een aanbeveling over de beste dosis van tromboseprofylaxe om toe te dienen aan COVID-19 patiënten die zijn opgenomen op de verpleegafdeling of de Intensive Care (IC). Hierover bestaat in de praktijk veel onduidelijkheid.

Uitgangsvraag

Wat is het antitrombotisch beleid bij patiënten met COVID-19?

Deze module is onderverdeeld in de volgende twee submodules:

1. Tromboseprofylaxe bij COVID-19 patiënten op de verpleegafdeling
2. Tromboseprofylaxe bij COVID-19 patiënten op de Intensive Care

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bedoeld voor ieder specialisme dat betrokken is bij tromboseprofylaxe bij COVID-19 patiënten die opgenomen zijn op de verpleegafdeling of de IC.

Voor patiënten

Patiënten met COVID-19 hebben een verhoogde kans op het krijgen van bloedstolsels in hun bloedvaten, wat kan leiden tot bijvoorbeeld trombose of een longembolie. Om deze reden wordt bij opname op de verpleegafdeling of de IC beschermende antistollingsmedicatie gegeven aan COVID-19 patiënten. Tot op heden is het onduidelijk welke dosis antistolling het beste is om toe te dienen. Deze richtlijnmodules gaan over de beste toe te dienen dosis antistollingsmedicatie aan patiënten met COVID-19 op de verpleegafdeling en de IC.

Zie ook de informatie op [Thuisarts.nl](https://www.thuisarts.nl):

<https://www.thuisarts.nl/corona/ik-heb-corona-en-krijg-behandeling-in-ziekenhuis>

Hoe is de richtlijn tot stand gekomen?

Op initiatief van de Federatie Medisch Specialisten is begin 2021 gestart met de ontwikkeling van de richtlijn COVID-19. Deze richtlijn beschrijft de infectiepreventie, diagnostiek, behandeling en revalidatie en nazorg voor alle COVID-19 (verdachte) patiënten. Deze richtlijn is deels gebaseerd op eerder gepubliceerde leidraden over COVID-19. In het voorjaar van 2020 is de leidraad 'COVID-19 coagulopathie' ontwikkeld op initiatief van de Nederlandse Internisten Vereniging (NIV). Deze leidraad is geüpdatet en doorontwikkeld tot een richtlijnmodule. Hiervoor is in 2020 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen die betrokken zijn bij de behandeling van patiënten met COVID-19. Daarnaast is er aandacht besteed aan het patiëntenperspectief door het meelesen van de patiëntenvereniging Harteraad. De verkregen input is meegenomen bij het opstellen van de module.

Verantwoording

Laatst beoordeeld : 09-02-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Tromboseprofylaxe op de verpleegafdeling bij COVID-19

Uitgangsvraag

Wat is de plaats van tromboseprofylaxe bij COVID-19 patiënten op de verpleegafdeling?

Aanbeveling

Geef antistolling aan patiënten met COVID-19 op de verpleegafdeling en overweeg hierbij een standaard profylactische of intermediaire dosis LMWH, omdat de huidige bewijslast geen overtuigende meerwaarde aantoonst van therapeutische antistolling.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen 1) behandeling met therapeutische dosis antistolling versus standaard of intermediaire dosis tromboseprofylaxe, en 2) behandeling met intermediaire dosis tromboseprofylaxe versus standaard dosis tromboseprofylaxe, bij patiënten met COVID-19 op de verpleegafdeling. Tot op heden zijn 5 RCTs gevonden die de vergelijking in de eerste PICO – therapeutische dosis versus standaard of intermediaire dosis - hebben onderzocht. Er zijn geen studies gevonden die de vergelijking in de tweede PICO – intermediaire dosis versus standaard dosis - hebben onderzocht. Voor de uitwerking van de studies is naast een analyse van alle studies samen een onderverdeling gemaakt tussen de interventie met *low-molecular-weight* heparines (LMWHs) en/of *ongefractioneerde* heparines (UFHs) en de interventie met directe orale anticoagulantia (DOACs).

Cruciale uitkomstmaten

Op basis van de gevonden resultaten zou het gebruik van een therapeutische dosis antistolling met een LMWH/UFH kunnen resulteren in geen tot een klein verschil in mortaliteit vergeleken met een standaard of intermediaire dosis tromboseprofylaxe met heparine. Daarentegen lijkt het effect van het gebruik van een therapeutische dosis antistolling met een DOAC vergeleken met een standaard of intermediaire dosis tromboseprofylaxe met heparine de andere kant op te gaan: dit zou kunnen resulteren in een verhoogde mortaliteit. De bewijskracht voor beide subgroepen is *laag*.

Voor de cruciale uitkomstmaat veneuze trombo-embolie is het onduidelijk of een behandeling met therapeutische dosis antistolling met een LMWH/UFH of DOAC zou kunnen leiden tot een reductie in het optreden van veneuze trombo-embolie. De bewijskracht hiervoor is *zeer laag*. Als naar alle trombo-embolische complicaties tezamen wordt gekeken, kan er worden geconcludeerd dat gebruik van een therapeutische dosis antistolling met een LMWH/UFH zou kunnen resulteren in geen tot een klein verschil in het optreden van trombo-embolische complicaties vergeleken met een standaard profylactische of intermediaire dosis heparine. De bewijskracht is *laag*. Het is onduidelijk of een behandeling met therapeutische dosis met een DOAC zou kunnen leiden tot een reductie in het optreden van trombo-embolische complicaties vergeleken met een standaard of intermediaire dosis profylaxe met LMWH/UFH. De bewijskracht hiervoor is *zeer laag*.

Hetzelfde patroon gaat op voor de cruciale uitkomstmaat ernstige bloeding. Voor deze uitkomstmaat kan

worden geconcludeerd dat het gebruik van een therapeutische dosis antistolling met een LMWH/UFH zou kunnen resulteren in geen tot een klein verschil in het optreden van een ernstige bloeding vergeleken met een standaard of intermediaire dosis tromboseprofylaxe met heparine. De bewijskracht is *laag*. Het is onduidelijk of een behandeling met therapeutische dosis met een DOAC zou kunnen leiden tot een toename in het optreden van een ernstige bloeding, vergeleken met een standaard of intermediaire dosis profylaxe met heparine. De bewijskracht hiervoor is *zeer laag*.

Belangrijke uitkomstmaten

Voor de belangrijke uitkomstmaat duur van ziekenhuis opname is geen bewijs gevonden voor de vergelijking tussen een therapeutische dosis met een LMWH/UFH en het gebruik van een standaard of intermediaire dosis tromboseprofylaxe met heparine. Voor de vergelijking tussen therapeutische dosis met een DOAC vergeleken met een standaard profylactische of intermediaire dosis heparine stelt de literatuur dat het gebruik van therapeutische dosis met een DOAC mogelijk zou kunnen resulteren in geen tot een klein verschil in de duur van ziekenhuis opname vergeleken met het gebruik van een standaard profylactische of intermediaire dosis heparine. De bewijskracht hiervoor was *redelijk*.

Voor opname op de intensive care unit (ICU) stelt de literatuur dat het gebruik van therapeutische dosis met een LMWH/UFH zou kunnen resulteren in geen tot een klein verschil in opname op de ICU vergeleken met het gebruik van een standaard of intermediaire dosis profylaxe met heparine. De bewijskracht hiervoor is *laag*. Er is geen bewijs gevonden voor de vergelijking tussen therapeutische dosis met een DOAC vergeleken met een standaard profylactische of intermediaire dosis met heparine.

Voor het aantal dagen overleving zonder orgaan ondersteuning stelt de literatuur dat het gebruik van therapeutische dosis met een LMWH/UFH zou kunnen resulteren in geen tot een klein verschil in het aantal dagen overleving zonder orgaan ondersteuning, vergeleken met het gebruik van een standaard of intermediaire dosis tromboseprofylaxe met heparine. De bewijskracht hiervoor is *redelijk*. Er is geen bewijs gevonden voor de vergelijking tussen therapeutische dosis met een DOAC vergeleken met een standaard of intermediaire dosis tromboseprofylaxe met heparine. Als wordt gekeken naar intubatie en mechanische ventilatie kan geconcludeerd worden dat het gebruik van zowel een therapeutische dosis met een LMWH/UFH als met een DOAC zou kunnen resulteren in geen tot een klein verschil in intubatie/mechanische ventilatie, vergeleken met het gebruik van een standaard of intermediaire dosis tromboseprofylaxe met heparine. De bewijskracht voor beide is *redelijk*.

Interpretatie

De interpretatie van de studies is om meerdere redenen complex. Er zijn geen studies gevonden die apart een therapeutische dosis met een intermediaire dosis tromboseprofylaxe met heparine vergeleken. Daarnaast zijn er ook geen studies die apart een intermediaire dosis met een standaard dosis tromboseprofylaxe met heparine hebben vergeleken. Daarom kan in de aanbeveling geen onderscheid worden gemaakt tussen de standaard dosis en intermediaire dosis tromboseprofylaxe met heparine. Voor bepaalde subgroepen, zoals leeftijd of D-dimeer niveau bij presentatie, kon geen onderscheid worden gevonden in de analyse van de studies. Daarom konden er geen specifieke aanbevelingen worden gedaan voor deze subgroepen. Alle drie de cruciale uitkomsten waren secundaire uitkomsten in de studies. De studies hadden samengestelde primaire eindpunten die onderling onvergelijkbaar bleken. Zo werden

bijvoorbeeld non-invasieve en invasieve beademing samen genomen, of sterfte en trombotische complicaties. Door deze verschillende samengestelde uitkomstmaten kon deze data niet gepoold worden. Verder zijn de studies in andere landen dan Nederland onder verschillende omstandigheden uitgevoerd. Het is bijvoorbeeld de vraag of de patiënten betrokken in studies die in andere landen zijn uitgevoerd (zoals Brazilië), vergeleken kunnen worden met Nederlandse patiënten. Een ander belangrijk punt van overweging is het feit dat de behandeling van patiënten met COVID-19 in 2021 in Nederland veranderd is ten opzichte van 2020, het jaar waarin de studies zijn verricht. Zo is er nu standaardbehandeling met hoge doses steroïden en IL-6 remmers. In verschillende van de gevonden studies kreeg een substantieel deel van de patiënten bijvoorbeeld geen behandeling met steroïden en werd slechts een kleine minderheid behandeld met IL-6 remmers. Alle studies hadden een zogenaamd 'open label design', waardoor bias kan zijn opgetreden bij zachtere uitkomstmaten als veneuze tromboembolie en bloeding. De artsen wisten welke behandeling een patiënt kreeg, hetgeen de klinische verdenking en diagnostische strategie heeft kunnen beïnvloeden. Eindpunten werden slechts deels centraal of lokaal geadjudiceerd, waardoor de validiteit van de diagnose longembolie (overgrote meerderheid van de trombotische events) niet in alle studies is na te gaan. De inclusiecriteria tussen de studies waren ook erg wisselend, met soms -maar niet altijd - selectie van patiënten met hoge tot zeer hoge D-dimeerwaarden. Patiënten met een van tevoren ingeschat hoog bloedingsrisico werden uitgesloten. De incidentie van bloedingscomplicaties zou daarom bij toepassing van therapeutische antistolling in de dagelijkse praktijk hoger kunnen uitvallen. Dit alles maakt dat er nog kennislacunes zijn. Het zal moeten blijken of resultaten van nieuwe studies de conclusies van de samenvatting van de literatuur zullen veranderen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Het doel van toedienen van antistolling is het voorkómen van veneuze en, in mindere mate, arteriële trombose. Er is geen verschil in toediening of impact van de standaard profylactische of intermediaire versus de therapeutische dosis LMWH; beide worden op dezelfde manier subcutaan geïnjecteerd. Er zijn geen subgroepen met andere uitkomsten gevonden.

Patiënten die een behandeling met medicijnen voor antistolling krijgen vinden complete en eenduidige informatievoorziening belangrijk, o.a. over de indicatie en de veiligheid en risico's van de behandeling (onderwerpen die van belang zijn in de communicatie met patiënten zijn terug te vinden in de Landelijke Transmurale Afspraak antistollingszorg (<https://lta-antistollingszorg.nl/communicatie-met-patienten>)).

Kosten (middelenbeslag)

Er is geen doorslaggevend verschil in de kosten voor de standaard profylactisch of therapeutisch gedoseerde LMWH of DOAC.

Aanvaardbaarheid, haalbaarheid en implementatie

Door de opzet en uitkomsten van de onderzochte studies is geen definitief bewijs gevonden voor de cruciale uitkomsten. In de door de werkgroep gevoerde discussies kwamen verschillende visies naar voren. Uiteindelijk was er volgens de werkgroep geen overtuigend bewijs om de aanbevelingen aan te passen, zoals geformuleerd in de leidraad COVID-19 coagulopathie van april 2020, en om het gebruik van therapeutische antistolling als standaardbehandeling aan te bevelen.

Rationale van de aanbeveling

De individuele studies hadden vaak gecombineerde uitkomstmaten, waarbij niet-invasieve beademing, IC opname, intubatie, trombotische complicaties, ECMO, CVVH en sterfte in verschillende combinaties waren samengenomen. Bij de analyses van de individuele eindpunten bleek het potentiële voordeel van therapeutische antistolling onder de van tevoren vastgestelde grens van klinische relevantie te liggen. Het effect van een therapeutische dosis antistolling werd derhalve niet klinisch relevant bevonden ten opzichte van een standaard profylactische- of intermediaire dosis antistolling. Eerder waren voor de Nederlandse situatie geen grenzen van klinische relevantie vastgesteld voor het instellen van tromboseprofylaxe. De werkgroep heeft zich bij het vaststellen van die grenzen geconformeerd aan de grenzen voor sterfte en IC opname, zoals vastgesteld door de SWAB werkgroep voor medicamenteuze behandeling van COVID-19. De grens voor een klinisch relevant verschil in trombotische complicaties werd indirect afgeleid uit de ACCP richtlijn tromboseprofylaxe uit 2012. Uit de onderzochte studies bleek ook dat therapeutische antistolling niet klinisch relevant meer schade berokkende dan een standaard profylactische- of intermediaire dosis: het optreden van bloedingen bleek niet klinisch relevant verschillend tussen de groepen. De werkgroep kwam na uitvoerige discussie in meerderheid, maar niet unaniem, tot de conclusie dat er geen grond is om af te wijken van de huidige standaard behandeling, zoals omschreven in de leidraad COVID-19 coagulopathie van april 2020 en de richtlijnmodules cardiovasculaire complicaties bij COVID-19 van maart 2021.

Onderbouwing

Achtergrond

Ondanks tromboseprofylaxe en een verbeterde behandeling van COVID-19 komen trombotische complicaties nog frequent voor, met een geschatte incidentie van 23-28% in ICU patiënten en 7-9 % in afdelingspatiënten (Jiménez, 2021; Tan, 2021; Nopp, 2021). Het is niet bekend wat de beste dosis van tromboseprofylaxe is (laag, intermediair of therapeutisch). Mede hierdoor verschillen ziekenhuisprotocollen.

Conclusies / Summary of Findings

1. Mortality

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Low GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs may result in little to no difference in mortality when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021; Marcos, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Low GRADE	Treatment with therapeutic anticoagulation with DOACs may result in an increase in mortality when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021</i>

Total group

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic anticoagulation on mortality when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021; Marcos, 2021; Lopes, 2021.</i>

2. Length of hospital stay

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

- GRADE	No studies were found that could answer the question what the effect is of therapeutic anticoagulation with LMWHs or UFHs when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs on hospital length of stay in adult COVID-19 patients admitted to the hospital ward (not ICU).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Moderate GRADE	Treatment with therapeutic anticoagulation with DOACs likely results in little to no difference in length of hospital stay when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021.</i>

3. ICU-admission (yes/no)

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Low GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs may result in little to no difference in ICU-admission when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Sholzberg, 2021; Marcos, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

- GRADE	No studies were found that could answer the question what the effect is of therapeutic anticoagulation with DOACs when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs on ICU-admission in adult COVID-19 patients admitted to the hospital ward (not ICU).

4. Organ support

Organ support free days

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Moderate GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs likely results in little to no difference in organ support free days when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Sholzberg, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

- GRADE	No studies were found that could answer the question what the effect is of therapeutic anticoagulation with DOACs when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs on organ support free days in adult COVID-19 patients admitted to the hospital ward (not ICU).

Organ support (intubation or mechanical ventilation)

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Moderate GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs likely results in little to no difference in organ support (intubation or mechanical ventilation) when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Moderate GRADE	Treatment with therapeutic anticoagulation with DOACs likely results in little to no difference in organ support (intubation or mechanical ventilation) when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021.</i>

Total group

Moderate GRADE	Treatment with therapeutic anticoagulation likely results in little to no difference in organ support (intubation or mechanical ventilation) when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021; Lopes, 2021.</i>

5. Venous thromboembolism

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Very low GRADE	The evidence is very uncertain about the effect of treatment with a therapeutic anticoagulation with LMWHs or UFHs on venous thromboembolism when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Sholzberg, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Very low GRADE	The evidence is very uncertain about the effect of treatment with a therapeutic anticoagulation with DOACs on venous thromboembolism when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021.</i>

Thromboembolic complications (VTE/ATE)

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Low GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs may result in little to no difference on thromboembolic complications (VTE/ATE) when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021; Marcos, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Very low GRADE	The evidence is very uncertain about the effect of treatment with a therapeutic anticoagulation with DOACs on thromboembolic complications (VTE/ATE) when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021.</i>

Total group

Low GRADE	Treatment with therapeutic anticoagulation may result in little to no difference on thromboembolic complications (VTE/ATE) when compared to standard prophylactic/intermediate anticoagulation LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Sholzberg, 2021; Marcos, 2021; Lopes, 2021.</i>

6. Major bleeding

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Low GRADE	Treatment with therapeutic anticoagulation with LMWHs or UFHs may result in little to no difference in major bleeding when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Spyropoulos, 2021; Sholzberg, 2021; Marcos, 2021.</i>

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Very low GRADE	The evidence is very uncertain about the effect of treatment with a therapeutic anticoagulation with DOACs on major bleeding when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Source: Lopes, 2021.</i>

Total group

Low GRADE	Treatment with therapeutic anticoagulation may result in little to no difference in major bleeding when compared to standard prophylactic/intermediate anticoagulation with LMWHs or UFHs in adult COVID-19 patients admitted to the hospital ward (not ICU). <i>Sources: Lawler, 2021; Spyropoulos, 2021; Sholzberg, 2021; Marcos, 2021; Lopes, 2021.</i>

Samenvatting literatuur

Description of studies: treatment with unfractionated or low-molecular-weight heparin in hospitalized COVID-19 patients

Lawler (2021) describes an open-label, international, adaptive, multiplatform RCT (mpRCT). In this mpRCT, three platforms (REMAPCAP, ATTACC and ACTIV-4a) evaluating therapeutic-dose anticoagulation with heparin were integrated. Patients were enrolled at 121 sites in 9 countries (the United States, Canada, the United Kingdom, Brazil, Mexico, Nepal, Australia, the Netherlands, and Spain) over a period of 8 months (April 2020-Jan 2021). A total of 1181 patients in the intervention group received a continuous intravenous therapeutic-dose anticoagulation with unfractionated or low-molecular-weight heparin up to 14 days or to hospital discharge and 1050 patients in the control group received usual-care thromboprophylaxis up to 14 days or hospital discharge (see evidence table for details about anticoagulation and thromboprophylaxis regimens). The study included hospitalized, non-critically ill COVID-19 patients, defined by the absence of critical care-level organ support at enrollment. The study population in the intervention group had a mean age of 59 years (SD 14.1) versus 58.8 years (SD 13.9) in the control group and the majority was male (60% in the intervention versus 57% in the control group). The study groups were balanced with respect to baseline characteristics. The length of follow-up was 28 to 90 days.

Spyropoulos (2021) describes a multicenter open label RCT evaluating the effects of therapeutic-dose low-molecular-weight heparin versus institutional standard prophylactic dose or intermediate-dose heparins for

thromboprophylaxis in high-risk hospitalized patients with COVID-19. Patients were enrolled from March 8, 2020, through May 14, 2021, at 12 centers in the US. A total of 11649 patients were assessed for eligibility. Eligible patients consisted of hospitalized nonpregnant adults 18 years or older with COVID-19 diagnosed by nasal swab or serologic testing. Moreover, there was a requirement for supplemental oxygen per investigator judgment and a plasma D-dimer level greater than 4 times the upper limit of normal based on local laboratory criteria or a sepsis-induced coagulopathy score of 4 or greater. Two hundred and fifty-seven patients were randomized into the therapeutic dose group ($n = 130$) or standard prophylactic/intermediate dose group ($n = 127$). However, a part of these patients were admitted to the intensive care unit (ICU): 45 out of 129 patients in the therapeutic dose group and 38 out of 124 in the standard prophylactic dose group. The results of the analyses of major bleeding were reported separately based on ICU status. Treatment began after randomization and was stopped at hospital discharge or upon occurrence of a primary efficacy outcome, key secondary outcome, or principal safety outcome requiring study drug discontinuation. All patients without a primary or key secondary outcome event underwent lower extremity Doppler compression ultrasonography at hospital day 10 + 4 or at discharge if sooner. The length of follow-up was 30 ± 2 days after randomization. Patients in the therapeutic dose group had a mean age of 65.8 years (SD 13.9) versus 67.7 years (SD 14.1) in the standard prophylactic dose group and the small majority was male (52.7% in the intervention versus 54.8% in the control group). The study groups were comparable with respect to baseline characteristics. Because of the relatively great number of patients that were admitted to the ICU, only the outcome measure major bleeding was included in the current analysis.

Sholzberg (2021) described a randomized controlled, adaptive, open label clinical trial evaluating the effects of therapeutic unfractionated or low-molecular-weight heparin compared with standard prophylactic unfractionated or low-molecular-weight heparin among moderately ill patients with covid-19 and increased D-dimer levels admitted to hospital wards. Elevated D-dimer levels were defined as one D-dimer value above the upper limit of normal (within 5 days (i.e. 120 hours) of hospital admission), and either D-Dimer ≥ 2 times the upper limit of normal, or D-Dimer above the upper limit of normal and oxygen saturation $\leq 93\%$ on room air. 465 adults were recruited between May 29, 2020, and April 12, 2021, at 28 hospitals in Brazil, Canada, Ireland, Saudi Arabia, United Arab Emirates, and the US. Eligible patients were randomized into the therapeutic dose heparin group ($n = 228$) or the standard prophylactic dose heparin group ($n = 237$). Treatments were continued until hospital discharge, day 28 of treatment, or death. Patients in the therapeutic dose group had a mean age of 60.4 years (SD 14.1) versus 59.6 years (SD 15.5) in the standard prophylactic dose group and the small majority was male (53.9% in the intervention versus 59.5% in the control group). The study groups were comparable with respect to baseline characteristics.

Marcos (2021) described an open-label, multicenter RCT in adult patients with non-severe COVID-19 pneumonia and elevated D-dimer > 500 ng/mL, who were hospitalized in a conventional ward. Patients were recruited and randomized at five Spanish hospitals. Patients were allocated to either the experimental arm ($n = 33$), which consisted of bemiparin treatment 115 IU/kg one a day, or the control arm ($n = 33$), which was standard prophylaxis with subcutaneous bemiparin 3,500 IU one a day. Treatments were continued for a period of 10 days, independently of hospital discharge. Patients in the intervention group had a mean age of 62.3 years (SD 12.2), versus 63.0 years (SD 13.7) in the control group. In the intervention group, the fast majority was male ($n = 24$, 72.7%), versus a small majority in the control group ($n = 17$, 53.1%). Overall, there was a good balance between both study arms.

Description of study: treatment with DOAC in hospitalized COVID-19 patients

Lopes (2021) described a pragmatic, open-label, multicenter RCT in patients hospitalized with COVID-19 and elevated D-dimer concentration (defined as D-dimer above the upper limit of normal) to assess whether in-hospital anticoagulation with rivaroxaban (20 mg once daily) for patients with a stable condition or enoxaparin (1 mg/kg twice daily) for patients with an unstable condition, followed by rivaroxaban for 30 days decreased the time to death, duration of hospitalization, or duration of supplemental oxygen support when compared with mainly in-hospital standard prophylactic dose anticoagulation with enoxaparin or unfractionated heparin. In total, 615 patients were allocated to receive the therapeutic anticoagulation or in-hospital standard prophylactic dose anticoagulation. Patients in the therapeutic group had a mean age of 56.7 years (SD 14.1), versus 56.5 years (SD 14.5) in the standard prophylactic group. The majority in both groups was male: 192 (62%) in the therapeutic group, versus 176 (58%) in the standard prophylactic dose group. At baseline, 23 out of 311 (7%) patients in the therapeutic dose group were defined as having a clinically unstable condition, versus 16 out of 304 (5%) patients in the standard prophylactic dose group. The study population contains a small number of clinically unstable patients (7%). This was taken into account when determining the level of evidence (indirectness).

Table 1. Overview of included RCTs that compared therapeutic dose anticoagulation with intermediate and/or standard dose anticoagulation in hospitalized COVID-19 patients, separated into subgroups

<i>Author, year and trial name</i>	<i>Intervention (I) and control (C)</i>	<i>Sample size for analysis</i>	<i>Doses of anticoagulants</i>	<i>Follow</i>
<u>Therapeutic dose vs intermediate/standard prophylactic dose – LMWH/UFH</u>				

Lawler, 2021 Randomised Open Label Clinical Trial by the ATTACC, ACTIV-4a, and REMAP- CAP investigators	I: Therapeutic dose with LMWH or UFH Patients may be switched between LMWH or UFH See supplement page 65 for actual Heparins Utilized and Dosage Adherence	I: N=1181 C: N=1050 Total = 2231	REMAP-CAP Dosed according to local hospital policy, practice, and guidelines for treatment of venous thromboembolism For UFH, suggested target for aPTT of 1.5 to 2.5 times the upper limit of normal or therapeutic anti- Xa levels. Low molecular weight heparin dosed according to patient weight.	ACTIV-4a LMWH dosed according to patient weight and creatinine clearance For UFH, suggested target of anti-Xa of 0.3-0.7 IU/ml or aPTT 1.5 to 2.5 times the upper limit of normal	ATTACC LMWH dosed according to patient weight and creatinine clearance according to local practice and policy For UFH, suggested target of aPTT 1.5 to 2.5 times the upper limit of normal or therapeutic anti- Xa levels	REMAI Up to ' hospita whiche first. For ICL therap anticoe could k discont dischar
	C: Usual-care thromboprophylaxis REMAP-CAP & ATTACC: Standard venous thromboprophylaxis according to local guidelines or usual practice ACTIV-4a: Any one of enoxaparin, dalteparin, tinzaparin, fondaparinux, or heparin according to local preference		REMAP-CAP Dose of chosen agent should not be sufficient to result in therapeutic anticoagulation	ACTIV-4a Dose of agent specified to be consistent with guidelines for low dose thromboprophylaxis	ATTACC Dose of chosen agent should not be more than half of the approved therapeutic dose for the treatment of venous thromboembolism	REMAI Up to ' hospita whiche first After tl decisio thromk are at c treating

Spyropoulos, 2021	I: therapeutic-dose LMWH (enoxaparin)	I: N= 129	I: 1 mg/kg subcutaneously twice daily if CrCl was 30 mL/min/1.73 m ² or greater or 0.5 mg/kg twice daily if CrCl was 15-29 mL/min/ 1.73 m ²	Study c hospita
HEP-COVID Randomized Open Label Clinical Trial	C: institutional standard prophylactic dose or intermediate-dose heparins for thromboprophylaxis	C: N= 124 Total = 253	C: could include UFH, up to 22 500 IU subcutaneously (divided twice or thrice daily); enoxaparin, 30 mg or 40 mg subcutaneously once or twice daily (weight based enoxaparin 0.5 mg/kg subcutaneously twice daily was permitted but strongly discouraged); or dalteparin, 2500 IU or 5000 IU subcutaneously daily	
Sholzberg, 2021	I: therapeutic heparin (LMWH or UFH) – Enoxaparin, dalteparin, fondaparinux, tinzaparin, UFH	I: N= 228 C: N= 237	Specific dosages specified in trial protocol for each type of heparin, depending on creatinine clearance and BMI. (see Table 1 and 2 supplementary file)	Therap Mean (Mediar
RAPID Randomised Open Label Clinical trial	C: standard prophylactic dose heparins (LMWH or UFH) – Enoxaparin, dalteparin, fondaparinux, tinzaparin, UFH	Total = 465		
Marcos, 2021	I: bemiparin	I: N= 33 C: N= 33	I: 115 IU/Kg once daily, adjusted to body weight (7,500 IU for patients between 50-70 Kg; 10,000 IU for patients weighing >70-100 Kg; 12,500 IU for patients who weighed >100 Kg).	The as indepe thromk case of it was a the stu
Randomised Open Label Clinical Trial	C: standard prophylaxis with subcutaneous bemiparin	Total: 66	C: 3,500 IU once daily	

Therapeutic dose vs intermediate/standard prophylactic dose – DOAC

Lopes, 2021 ACTION Randomised Open Label Clinical trial	I: therapeutic anticoagulation	I: N= 311	I: Clinically stable patients = 20 mg once daily. A reduced dose of 15 mg once daily was used in patients with a creatinine clearance of 30–49 mL/min or those taking azithromycin.	All patients continued on rivaroxaban
	Clinically stable patients = oral rivaroxaban Clinically unstable patients = subcutaneous enoxaparin or intravenous UFH	C: N= 304 Total: 615	Clinically unstable patients = subcutaneous enoxaparin at a dose of 1 mg/kg twice per day, intravenous unfractionated heparin at a dose to achieve a target anti-Xa concentration (0.3–0.7 IU/mL) or a corresponding target activated partial thromboplastin time (1.5–2.5 times the mean normal value). Unfractionated heparin was the preferred option for patients with renal dysfunction or disseminated intravascular coagulation. When these patients became stable, they were transitioned to oral rivaroxaban (20 mg or 15 mg).	
	C: standard prophylactic dose anticoagulation – standard venous thromboembolism prophylaxis with enoxaparin or UFH during hospitalisation. Patients in this group could receive therapeutic anticoagulation if they developed a definitive clinical indication or at the discretion of the investigator if a high clinical suspicion of a thromboembolic event was raised and a confirmatory test was not available.		C:?	

LMWH: low-molecular weight heparin; UFH: unfractionated heparin.

Table 2. Overview of composite outcomes and results per study

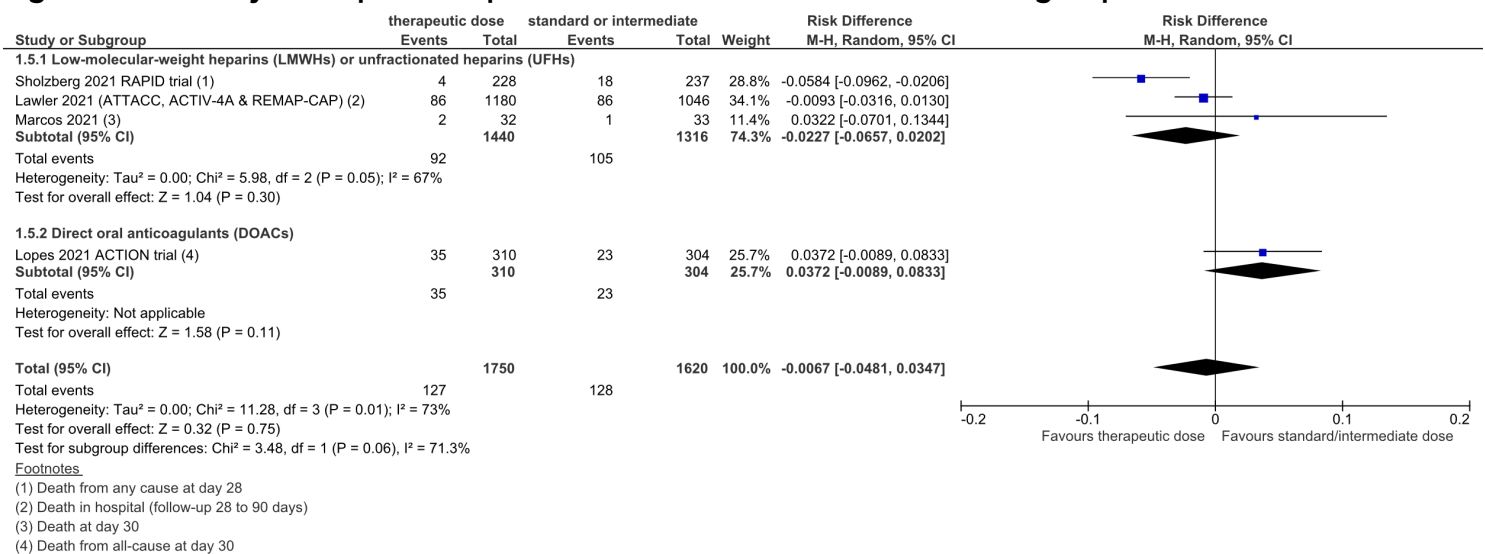
<i>Study</i>	<i>Primary composite outcome</i>	<i>Results</i>
Lawler (2021) Multiplatform trial	Organ support free days as evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge.	1. Because the majority of patients in the two treatment groups survived until hospital discharge without receipt of critical care–level organ support, the median value for organ support–free days was 22 in both groups. 2. Out of 1048 patients in the standard prophylactic dose heparin group, 801 (76.4%) survived until hospital discharge without organ support during the first 21 days, as compared to 939 of 1171 patients (80.2%) in the therapeutic dose heparin group. The RD was 3.8% in favor of the therapeutic dose group (95%CI 0.3% to 7.2%).
Sholzberg (2021) RAPID trial	1. A composite of ICU admission, non-invasive (bilevel or continuous positive airway pressure) or invasive mechanical ventilation, or death up to 28 days 2. A composite of death or any mechanical ventilation 3. A composite of death or ICU admission	1. In the therapeutic dose heparin group, 37 out of 228 (16.2%) patients reported the primary composite outcome, versus 52 out of 237 (21.9%) patients in the standard prophylactic dose heparin group. The RD was 5.7% in favor of the therapeutic dose heparin group (95%CI -12.8% to 1.4%). 2. In the therapeutic dose heparin group, 22 out of 228 (9.6%) patients reported the composite outcome, versus 37 out of 237 (15.6%) patients in the standard prophylactic dose heparin group. 3. In the therapeutic dose heparin group, 35 out of 228 (15.4%) patients reported the composite outcome, versus 49 out of 237 (20.7%) patients in the standard prophylactic dose heparin group.
Spyropoulos (2021) HEP-COVID trial	A composite of VTE, ATE, or death for the non-ICU stratum separately	In the therapeutic dose heparin group, 14 out of 84 (16.7%) patients reported the composite outcome, versus 31 out of 86 (36.1%) patients in the standard prophylactic dose heparin group. The RD was 19.4% in favor of the therapeutic dose heparin group (95%CI -32.3% to 6.5%).

Marcos (2021) BEMICOP trial	A composite of death, admission at ICU, need of mechanical ventilation support, development of moderate/severe acute respiratory distress syndrome and venous or arterial thrombosis within 10 days	In the therapeutic dose bemiparin group, 7 out of 32 (21.9%) patients reported the composite outcome, versus 6 out of 33 (18.2%) patients in the standard prophylactic dose bemiparin group. The RD was 3.7% in favor of the standard prophylactic dose bemiparin group (95%CI -15.8% to 23.1%).
Lopes (2021) ACTION trial	A composite outcome of time to death, duration of hospitalisation, or duration of supplemental oxygen use	The win ratio for the stable patients stratum was 0.84 (95%CI 0.57 to 1.21), indicating a worse outcome in the therapeutic dose group.

Results

1. Mortality

Figure 1: Mortality in hospitalized patients with COVID-19, divided in subgroups



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

A total of 92 out of 1440 (6.4%) patients died in the therapeutic dose group, versus 105 out of 1316 (8.0%) in the standard prophylactic/intermediate dose group. The pooled risk difference (RD) was 2.3% in favor of the therapeutic dose group (95%CI -6.6% to 2.0%; figure 1). The corresponding NNT was 44. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure mortality was downgraded from high to **low** because of heterogeneity in the effect size (inconsistency, -1), and the confidence interval of the pooled RD crossing the lower threshold for clinical relevance (imprecision, -1).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

A total of 35 out of 310 (11%) patients died in the therapeutic dose group, versus 23 out of 304 (8%) in the standard prophylactic/intermediate dose group. The pooled RD was 3.7% in favor of the standard prophylactic/intermediate dose group (95%CI -0.9% to 8.3%; figure 1). The corresponding NNT was 27. This was considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure mortality was downgraded from high to **low** because of the inclusion of a small number of patients admitted to the ICU (indirectness, -1), the inclusion of a single study and the confidence interval of the pooled RD crossing the upper threshold for clinical relevance (imprecision, -1).

Total group

Overall, 127 out of 1750 (7.3%) patients died in the therapeutic dose group, versus 128 out of 1620 (7.9%) in the standard prophylactic/intermediate dose group. The pooled RD was 0.7% in favor of the therapeutic dose group (95%CI -4.8% to 3.5%; figure 1). The corresponding NNT was 149. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure mortality was downgraded from high to **very low** because of heterogeneity in effect size (inconsistency, -1), and the confidence interval of the pooled RD crossing both thresholds (upper and lower) for clinical relevance (imprecision, -2).

2. Length of hospital stay

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

None of the studies reported length of hospital stay in both study groups.

However, Lawler (2021) did report the length of hospital stay for the total group of patients. The median hospital length of stay for all patients was 5 days (interquartile range 3-10). Lawler (2021) also reported an adjusted (age, sex, site, D-dimer group, and time epoch) hazard ratio of the time-to-event endpoint length of hospital stay truncated at 28 days of 1.03 (95%CI 0.95 to 1.13) in favor of the group treated with a therapeutic dose anticoagulation.

Sholzberg (2021) reported the number of hospital-free days alive. The mean number of hospital-free days alive was 19.8 days (SD 7.3) in the therapeutic dose group versus 18.4 (SD 9.2) in the standard prophylactic dose group. The mean difference was 1.40 days (95%CI -0.11 to 2.91).

Marcos (2021) reported hospital discharge in the first 10 days. In the therapeutic dose group, 21 out of 32 patients (65.6%) were discharged, versus 26 out of 33 patients (78.8%) in the standard prophylactic dose group.

Level of evidence

The level of evidence could not be determined, as none of the studies reported on length of hospital stay.

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Lopes (2021) reported length of hospital stay at the end of 30 days. The mean length of stay was 8.1 days (SD 7.2) for the therapeutic dose group, versus 7.8 days (SD 7.5) for the standard prophylactic dose group. The mean difference was 0.3 days (95%CI -0.86 to 1.46). This difference was not considered to be clinically relevant.

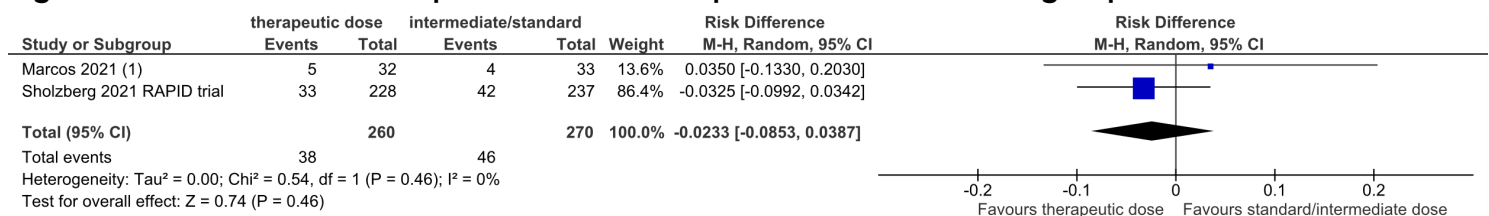
Level of evidence

The level of evidence regarding the outcome measure length of hospital stay was downgraded from high to **moderate** because of the low number of patients (imprecision, -1).

3. ICU-admission (yes/no)

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Figure 2: ICU-admission in hospitalized COVID-19 patients, divided in subgroups.



Footnotes

(1) Need of ICU at day 30

Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Sholzberg (2021) reported ICU-admission. 33 out of 228 (14.5%) patients in the therapeutic dose group were admitted to the ICU, versus 42 out of 237 (17.7%) in the standard prophylactic dose group.

Marcos (2021) reported the need of ICU at day 10 and day 30. At day 10, 4 out of 32 patients (12.5%) needed ICU in the therapeutic dose group, versus 4 out of 33 patients (12.1%) in the standard prophylactic dose group. At day 30, 5 out of 32 patients (15.6%) needed ICU in the therapeutic dose group, versus 4 out of 33 patients (12.1%) in the standard prophylactic dose group.

Taken together, the pooled RD was 2.3% in favor of the therapeutic dose group (95%CI -8.5% to 3.9%, figure 2). The corresponding NNT was 43. This was not considered to be a clinically relevant difference.

Lawler (2021) did not report ICU-admission.

Level of evidence

The level of evidence regarding the outcome measure ICU-admission was downgraded from high to **low** because of the low number of events and the confidence interval around the pooled RD crossing the lower threshold for clinical relevance (imprecision, -2).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Lopes (2021) did not report information on ICU-admission.

4. Organ support

Organ support free days

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Sholzberg (2021) reported organ support free days alive. In the therapeutic dose group, patients had a mean of 25.8 (SD 6.2) organ support free days alive versus 24.1 (SD 8.8) days in the standard prophylactic dose group. The mean difference was 1.70 (95%CI 0.32 to 3.08) in favor of the therapeutic heparin group. This difference was not considered to be clinically relevant.

Lawler (2021) reported the organ support free days as evaluated on an ordinal scale that combined in-hospital death and the number of days free of cardiovascular or respiratory organ support up to day 21 among patients who survived to hospital discharge. Because the majority of patients in the two treatment groups survived until hospital discharge without receipt of critical care-level organ support, the median value for organ support-free days was 22 in both groups. Out of 1048 patients in the standard prophylactic dose group, 801 (76.4%) survived until hospital discharge without organ support during the first 21 days, as compared to 939 of 1171 patients (80.2%) in the therapeutic dose group. The RD was 3.8% in favor of the therapeutic dose group (95%CI 0.3% to 7.2%). However, no conclusions can be drawn based on this data.

Marcos (2021) did not report organ support free days as a separate outcome that matched how the working group defined it a priori, but solely as part of the primary composite outcome.

Level of evidence

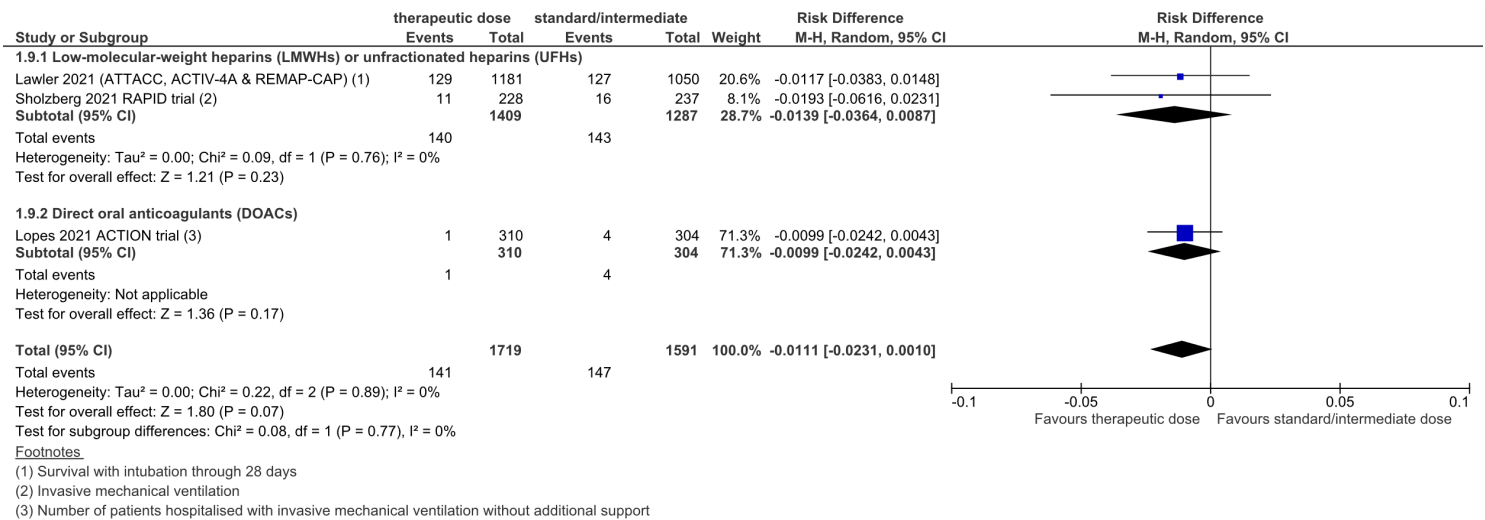
The level of evidence regarding the outcome measure organ support free days (based on data from Sholzberg (2021)) was downgraded from high to **moderate** because of the confidence interval around the mean difference crossing the upper threshold for clinical relevance (imprecision, -1).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Lopes (2021) did not report organ support free days.

Organ support (intubation or mechanical ventilation)

Figure 3: intubation or mechanical ventilation in hospitalized COVID-19 patients, divided in subgroups.



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Lawler (2021) originally reported survival without intubation through 28 days. This was recalculated to survival with intubation through 28 days.

A total of 140 out of 1409 (9.9%) patients received intubation or invasive mechanical ventilation in the therapeutic dose group, versus 143 out of 1287 (11.1%) in the standard prophylactic/intermediate dose group. The pooled risk difference (RD) was 1.4% in favor of the therapeutic dose group (95%CI -3.6% to 0.9%; figure 3). The corresponding NNT was 72. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure organ support (intubation or mechanical ventilation) was downgraded from high to **moderate**, because of the small number of events (imprecision, -1).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

A total of 1 out of 310 (0.3%) patients received invasive mechanical ventilation without additional support in the therapeutic dose group, versus 4 out of 304 (1.3%) in the standard prophylactic/intermediate dose group. The pooled risk difference (RD) was 1.0% in favor of the therapeutic dose group (95%CI -2.4% to 0.4%; figure 3). The corresponding NNT was 101. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure organ support (intubation or mechanical ventilation) was downgraded from high to **moderate**, because of the small number of events (imprecision, -1).

Total group

A total of 141 out of 1719 (8.2%) patients received intubation or invasive mechanical ventilation in the therapeutic dose group, versus 147 out of 1591 (9.2%) in the standard prophylactic/intermediate dose group. The pooled risk difference (RD) was 1.1% in favor of the therapeutic dose group (95%CI -2.3% to 0.1%; figure 3). The corresponding NNT was 90. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure organ support (intubation or mechanical ventilation) was downgraded from high to **moderate**, because of the small number of events (imprecision, -1).

5. Venous thromboembolism

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Sholzberg (2021) reported the **number of patients** with venous thromboembolism (consisting of deep vein thrombosis and pulmonary embolism). In the therapeutic dose group, 2 out of 228 patients (0.9%) developed venous thromboembolism, versus 6 out of 237 (2.5%) in the standard prophylactic dose group. The RD was 1.7% in favor of the therapeutic dose group (95%CI -4.0% to 0.7%). The corresponding NNT was 61. This difference was not considered to be clinically relevant.

Lawler (2021) and Marcos (2021) did not report the number of patients with venous thromboembolism.

However, Lawler (2021) did report the number of **events** for deep venous thrombosis and pulmonary embolism separately. In the therapeutic dose group 6 events for deep venous thrombosis were reported, versus 7 events in the standard prophylactic dose group. For pulmonary embolism, 10 events were reported in the therapeutic dose group, versus 19 events in the standard prophylactic dose group.

Level of evidence

The level of evidence (based on data from Sholzberg (2021)) regarding the outcome measure venous thromboembolism was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), the inclusion of one study with a small number of events (imprecision, -2).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

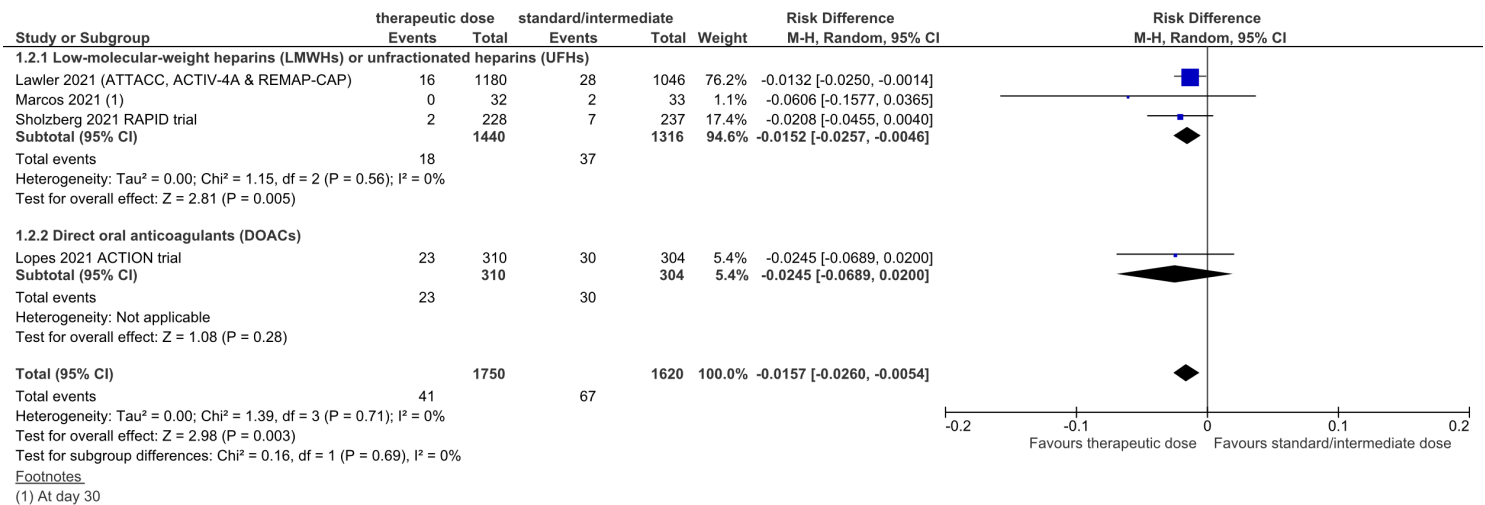
Lopes (2021) reported the number of patients with venous thromboembolism (consisting of deep vein thrombosis and pulmonary embolism). 11 out of 310 (3.6%) patients in the therapeutic dose group versus 18 out of 304 (5.9%) patients in the standard prophylactic dose group developed venous thromboembolism. The RD was 2.4% in favor of the therapeutic dose group (95%CI -5.7% to 1.0%). The corresponding NNT was 42. This difference was not considered to be clinically relevant.

Level of evidence

The level of evidence regarding the outcome measure venous thromboembolism was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), the inclusion of patients admitted to the ICU (indirectness, -1), the inclusion of only one study with a limited number of events and the confidence interval around the RD crossing the lower threshold for clinical relevance (imprecision, -1).

Thromboembolic complications (VTE/ATE)

Figure 4: thromboembolic complications in hospitalized COVID-19 patients, divided in subgroups.



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

Lawler (2021) reported the number of patients with an in-hospital thrombotic event (defined as pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, systemic arterial thromboembolism, and deep venous thrombosis): 16 out of 1180 (1.5%) patients experienced an in-hospital thrombotic event in the therapeutic dose group, versus 28 out of 1046 (2.7%) in the standard prophylactic dose group.

Sholzberg (2021) reported venous and arterial thromboembolism separately. When combined, 2 out of 228 (0.9%) patients developed VTE/ATE in the therapeutic dose heparin group, versus 7 out of 237 (3.0%) patients in the standard prophylactic dose heparin group.

Marcos (2021) reported arterial and venous thromboembolism (ATE/VTE) combined in one outcome measure at day 10 and day 30. At day 10, none of the patients in the intervention group developed ATE/VTE, versus 1 out of 33 patients (3.0%) in the control group. At day 30, none of the patients in the intervention group had developed ATE/VTE, versus 2 out of 33 patients (6.1%) in the control group.

Overall, the pooled RD was 1.5% in favor of the therapeutic dose heparin group (95%CI -2.6% to 0.5%, figure 4). The NNT was 66. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure thromboembolic complications was downgraded from high to **low** because of the open-label study designs (risk of bias, -1), and the small number of events (imprecision, -1).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

Lopes (2021) also reported the number of patients with the composite thrombotic outcome (consisting of venous thromboembolism – deep vein thrombosis and pulmonary embolism, myocardial infarction, ischemic stroke, and major adverse limb event). 23 out of 310 (7.4%) patients in the therapeutic dose group versus 30

out of 304 (9.9%) patients in the standard prophylactic dose group reported the composite thrombotic outcome. The RD was 2.5% in favor of the therapeutic dose DOAC group (95%CI -6.9% to 2.0%, figure 4). The NNT was 41. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure thromboembolic complications was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), the inclusion of patients admitted to the ICU (indirectness, -1), and the confidence interval around the RD crossing the lower threshold for clinical relevance (imprecision, -1).

Total group

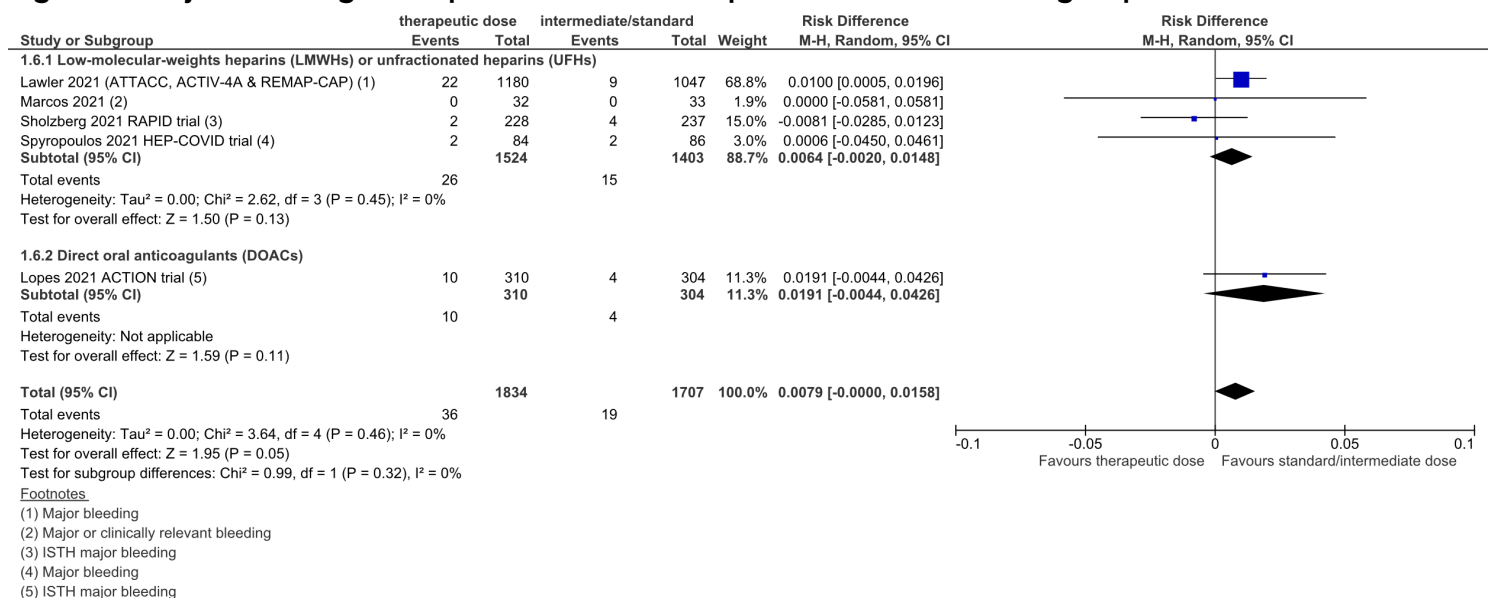
In total, 41 out of 1750 (2.3%) patients in the therapeutic dose group developed thromboembolic complications, versus 67 out of 1620 (4.1%) patients in the standard prophylactic/intermediate dose group. The pooled RD was 1.6% in favor of the therapeutic dose group (95%CI -2.6% to -0.5%; figure 4). The corresponding NNT was 64. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure thromboembolic complications was downgraded from high to **low** because of the open-label study designs (risk of bias, -1), and the low number of events (imprecision, -1).

6. Major bleeding

Figure 5: Major bleeding in hospitalized COVID-19 patients, divided in subgroups.



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

Therapeutic dose LMWHs/UFHs vs intermediate/standard prophylactic dose anticoagulation LMWHs/UFHs

In total, 26 out of 1524 (1.7%) patients in the therapeutic dose group developed major bleeding, versus 15 out of 1403 (1.1%) patients in the standard prophylactic/intermediate dose group. The pooled RD was 0.6% in favor of the standard prophylactic/intermediate dose group (95%CI -0.2% to 1.5%; figure 5). The

corresponding NNH was 156. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure major bleeding was downgraded from high to **low** because of the open-label study designs (risk of bias, -1), and the low number of cases (imprecision, -1).

Therapeutic dose DOACs vs intermediate/standard prophylactic dose LMWHs/UFHs

In total, 10 out of 310 (3%) patients in the therapeutic dose group developed major bleeding, versus 4 out of 304 (1%) patients in the standard prophylactic/intermediate dose group. The RD was 1.9% in favor of the standard prophylactic/intermediate dose group (95%CI -0.4% to 4.3%, figure 5). The corresponding NNH was 52. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure major bleeding was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), heterogeneity in the study population (indirectness, -1), inclusion of one study with a low number of cases (imprecision, -1).

Total group

In total, 36 out of 1834 (2.0%) patients in the therapeutic dose group developed major bleeding, versus 19 out of 1707 (1.1%) patients in the standard prophylactic/intermediate dose group. The pooled RD was 0.8% in favor of the standard prophylactic/intermediate dose group (95%CI 0.0% to 1.6%; figure 5). The corresponding NNH was 127. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure major bleeding was downgraded from high to **low** because of the open-label study designs (risk of bias, -1), and the low number of events (imprecision, -1).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the efficacy and safety of anticoagulation therapy in COVID-19 patients admitted to the hospital (not ICU)?

PICO 1

P: all adult COVID-19 patients admitted to the hospital (not ICU) who are not already on chronic therapeutic anticoagulants

I: therapeutic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

C: standard prophylactic dose or intermediate dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) or no use of standard prophylactic dose or intermediate dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

O: mortality, major bleeding, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined), length of hospital stay, ICU-admission (yes/no) and organ support free days

PICO 2

P: all adult COVID-19 patients admitted to the hospital (not ICU) who are not already on chronic therapeutic anticoagulants

I: intermediate dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

C: standard prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) or no use of standard prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

O: mortality, major bleeding, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined), length of hospital stay, ICU-admission (yes/no) and organ support free days

When possible subgroup analyses were performed to evaluate the efficacy and safety of the different types of anticoagulant.

We searched for standard dose of prophylaxis and intermediate dose of prophylaxis; the latter is typically a doubling of the standard dose of prophylaxis.

Relevant outcome measures

The guideline development group considered mortality, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined) and major bleeding as critical outcome measures for decision making; and length of hospital stay, ICU-admission (yes/no), and organ support as important outcome measures for decision making.

A priori, the working group did not define organ support but used the definitions used in the studies.

The working group defined a risk difference of 3% as a minimal clinically (patient) important difference for mortality, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined) and major bleeding; 3 days for length of hospital stay and organ support free days; and a risk difference of 5% for ICU-admission (yes/no) and a risk difference of 5% for organ support (yes/no).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until October 18th 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 686 hits. Studies were selected based on the following criteria:

- randomized controlled trial (RCT)
- peer reviewed and published in indexed journal or pre-published
- comparing treatment with

1. a therapeutic dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) with a standard prophylactic dose, intermediate dose, or no dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)
 2. an intermediate dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) with a standard prophylactic dose or no dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)
- in non-critically ill patients with COVID-19
 - <10% of patients admitted to the ICU.

Fourteen studies were initially selected based on title and abstract screening. After reading the full text, nine studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies were included.

Results

Five studies were included in the analysis of the literature. All studies investigated a therapeutic dose anticoagulant versus standard prophylactic or intermediate dose anticoagulant in COVID-19 patients admitted to the hospital (PICO 1). No studies were found that investigated intermediate dose anticoagulant versus standard prophylactic dose anticoagulant in COVID-19 patients admitted to the hospital (PICO 2). One of the studies included a small number of patients admitted to the ICU. Subgroups were made based on the type of anticoagulant used: low-molecular-weight heparins (LMWHs) and unfractionated heparins (UFHs), or direct oral anticoagulants (DOACs). Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 09-02-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Tromboseprofylaxe op de Intensive Care

Uitgangsvraag

Wat is de plaats van tromboseprofylaxe bij COVID-19 patiënten op de intensive care?

Aanbeveling

Geef een standaard profylactische dosis antistolling aan patiënten met COVID-19 op de intensive care.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de verschillen in klinische uitkomsten tussen 1) behandeling met therapeutische dosis antistolling versus standaard of intermediaire dosis tromboseprofylaxe, en 2) behandeling met intermediaire dosis tromboseprofylaxe versus standaard dosis tromboseprofylaxe, bij patiënten met COVID-19 op de intensive care (IC). Tot op heden zijn 3 RCTs gevonden die de vergelijking in de eerste PICO – therapeutische dosis versus profylactische of intermediaire dosis - hebben onderzocht. Er is één studie gevonden, waarvan de resultaten op twee meetmomenten in twee artikelen beschreven werden, die de vergelijking in de tweede PICO – intermediaire dosis versus profylactische dosis - heeft onderzocht. Tabel 1 geeft een overzicht van voorbeelddoseringen voor drie soorten *low-molecular-weight* heparines (LMWHs).

Tabel 1. Voorbeelddoseringen voor de meest gebruikte LMWHs in Nederland

	Doseringen		
	Nadroparine	Dalteparine	Enoxaparine
Standaard profylactische dosering	2850 IU eenmaal daags	2500 IU eenmaal daags	20 mg eenmaal daags
Intermediair profylactische dosering	5700 IU eenmaal daags (of 2 dd 2850 IU)	5000 IU eenmaal daags	40 mg eenmaal daags
Therapeutische dosering	11.400 IU per dag voor gewicht tussen 50 en 70 kg; 15.200 IU per dag voor gewicht boven de 70 kg; en 17.100 IU per dag voor gewicht boven de 90 kg	200 IU per kg per dag met een maximum van 18.000 IU per dag	1,5 mg per kg per dag of 1,0 mg tweemaal daags

LMWH, *low-molecular-weight heparin*; IU, *International Unit*.

Cruciale uitkomstmaten

Voor de cruciale uitkomstmaten mortaliteit, veneuze trombo-embolie, en het aantal dagen vrij van mechanische ventilatie is het op basis van de gevonden resultaten onzeker of het gebruik van een therapeutische dosis antistolling zou kunnen resulteren in een verschil in deze uitkomstmaten, vergeleken

met een profylactische dosis antistolling. Hetzelfde geldt voor de vergelijking tussen een intermediaire dosis en profylactische dosis antistolling. De bewijskrachten voor beide vergelijkingen waren voor deze drie uitkomstmaten *zeer laag*.

Voor trombo-embolische complicaties samengenomen (arteriële en veneuze trombo-embolie) werd gevonden dat behandeling met een therapeutische dosis antistolling mogelijk kan resulteren in een reductie in trombo-embolische complicaties vergeleken met een profylactische dosis antistolling. De bewijskracht hiervoor was *laag*. Het is onduidelijk of een intermediaire dosis antistolling zou kunnen leiden tot een verschil in trombo-embolische complicaties vergeleken met een profylactische dosis antistolling. De bewijskracht was *zeer laag*.

Behandeling met therapeutische dosis antistolling zou kunnen resulteren in geen tot een klein verschil in ernstige bloedingen vergeleken met een profylactische of intermediaire dosis antistolling. De bewijskracht hiervoor was *laag*. Het is onduidelijk of behandeling met een intermediaire dosis antistolling zou ook kunnen resulteren in een verschil in ernstige bloedingen vergeleken met een profylactische dosis antistolling. De bewijskracht hiervoor was *zeer laag*.

Belangrijke uitkomstmaten

Voor de belangrijke uitkomstmaat duur van ziekenhuisopname is het onduidelijk of behandeling met een therapeutische dosis antistolling zou kunnen resulteren in een verschil in de duur van ziekenhuisopname vergeleken met een profylactische dosis antistolling. De bewijskracht hiervoor was *zeer laag*. Er is geen bewijs gevonden voor het effect van een intermediaire dosis antistolling vergeleken met een profylactische dosis antistolling op de duur van ziekenhuisopname. Voor de duur van IC opname is het ook onduidelijk of behandeling met een therapeutische dosis antistolling zou kunnen resulteren in een verschil in de duur van IC opname vergeleken met een profylactische dosis antistolling. Hetzelfde geldt voor de vergelijking tussen een intermediaire dosis antistolling vergeleken met een profylactische dosis antistolling. De bewijskracht voor beide vergelijkingen was *zeer laag*.

Er is geen bewijs gevonden voor het effect van een therapeutische dosis antistolling vergeleken met een profylactische dosis antistolling op orgaan support anders dan mechanische ventilatie. Het is onduidelijk of behandeling met een intermediaire dosis antistolling vergeleken met een profylactische dosis antistolling zou kunnen resulteren in een verschil in orgaan support anders dan mechanische ventilatie, meer specifiek nier vervangende therapie. De bewijskracht hiervoor was *zeer laag*.

Er is geen bewijs gevonden voor het effect op het aantal dagen vrij van orgaan ondersteuning anders dan mechanische ventilatie voor de vergelijking tussen 1) een therapeutische dosis antistolling vergeleken met een profylactische dosis antistolling, en 2) een intermediaire dosis antistolling vergeleken met een profylactische dosis antistolling. Voor de uitkomstmaten heparine geïnduceerde trombocytopenie en cumulatieve transfusie zijn geen resultaten beschreven in de geselecteerde studies.

Interpretatie

De interpretatie van de studies is om meerdere redenen complex. De INSPIRATION studie komt qua populatie niet overeen met de Nederlandse populatie op de Intensive Care Unit (ICU), gezien het relatief

lage percentage invasieve beademing (dat samengenomen met non-invasieve beademing rond de 50% lag) en de lage APACHE II score van de geïnccludeerde patiënten (mediaan 8, IQR 5-11). In de multiplatform studie van Goligher (2021) is dit percentage ook laag, maar daar kregen patiënten *high flow nasal oxygen* of *non invasive ventilation* en slechts 1,5% van de patiënten zuurstof via masker of *low flow nasal oxygen*. Ook was de APACHE II score beduidend hoger (mediaan 14, IQR 8-21), hetgeen meer in lijn is met de Nederlandse situatie op de ICU. De studie van Lemos (2020) uit Brazilië met tweemaal 10 patiënten is heel klein en daarom niet representatief. Met betrekking tot bepaalde subgroepen, zoals leeftijd of D-dimeer niveau bij presentatie, kon geen onderscheid worden gevonden in de analyse van de studies. Daarom konden geen aanbevelingen worden gedaan voor deze subgroepen. Alle cruciale uitkomsten waren secundaire uitkomsten in de studies. De studies hadden samengestelde primaire eindpunten die onderling onvergelijkbaar bleken. Zo werden bijvoorbeeld non-invasieve en invasieve beademing samen genomen, of sterfte en trombotische complicaties. Door deze verschillende samengestelde uitkomstmaten kon deze data niet gepoold worden. Een ander belangrijk punt van overweging is het feit dat de behandeling van patiënten met COVID-19 in 2021 in Nederland veranderd is ten opzichte van 2020, het jaar waarin de studies zijn verricht. Zo is er nu standaardbehandeling met IL-6 remmers en monoklonale antistoffen. In verschillende van de gevonden studies kreeg een substantieel deel van de patiënten bijvoorbeeld geen behandeling met steroïden en werd slechts een kleine minderheid behandeld met IL-6 remmers. Alle studies hadden een zogenaamd 'open label design', waardoor bias kan zijn opgetreden bij zachtere uitkomstmaten als veneuze trombo-embolie en bloeding. De artsen wisten welke behandeling een patiënt kreeg, hetgeen de klinische verdenking en diagnostische strategie heeft kunnen beïnvloeden. Eindpunten werden slechts deels centraal of lokaal geadjudiceerd, waardoor de validiteit van de diagnose longembolie (overgrote meerderheid van de trombotische events) niet in alle studies is na te gaan. De inclusiecriteria tussen de studies waren ook erg wisselend, met soms -maar niet altijd - selectie van patiënten met hoge tot zeer hoge D-dimeerwaarden. Patiënten met een van tevoren ingeschat hoog bloedingsrisico werden uitgesloten. De incidentie van bloedingscomplicaties zou daarom bij toepassing van therapeutische antistolling in de dagelijkse praktijk hoger kunnen uitvallen. Naast beademing was er voor andere orgaanondersteuning (zoals nierfunctievervangende therapie en extracorporele membraanoxygenatie (ECMO)) alleen literatuur beschikbaar met een zeer lage bewijskracht. Wat betreft veiligheid was er alleen rapportage van bloedingen en niet van cumulatieve transfusie, en kan er niet uitgesloten worden dat er een onderrapportage is geweest van milde bloedingscomplicaties. Ook is er geen data gerapporteerd over het voorkomen van van heparine geïnduceerde trombocytopenie (HIT). Dit alles maakt dat er nog kennislacunes zijn. Het zal moeten blijken of resultaten van nieuwe studies de conclusies van de samenvatting van de literatuur zullen veranderen.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Het doel van toedienen van antistolling is het voorkómen van veneuze en, in mindere mate, arteriële trombose. Er is geen verschil in toediening of impact van de profylactische of intermediaire versus de therapeutische dosis LMWH; beide worden op dezelfde manier subcutaan geïnjecteerd. Er zijn geen subgroepen met andere uitkomsten gevonden.

Patiënten die een behandeling met medicijnen voor antistolling krijgen vinden complete en eenduidige informatievoorziening belangrijk, o.a. over de indicatie en de veiligheid en risico's van de behandeling (onderwerpen die van belang zijn in de communicatie met patiënten zijn terug te vinden in de Landelijke Transmurale Afspraak antistollingszorg (<https://lta-antistollingszorg.nl/communicatie-met-patienten>)).

Kosten (middelenbeslag)

Er is geen doorslaggevend verschil in de kosten voor de profylactisch of therapeutisch gedoseerde LMWH of ongefractioneerde heparine.

Aanvaardbaarheid, haalbaarheid en implementatie

Door de opzet en uitkomsten van de onderzochte studies is geen definitief bewijs gevonden voor de cruciale uitkomsten. Het was volgens de werkgroep onzeker of het gebruik van therapeutische of intermediaire dosis antistolling tot een klinisch relevant verschil in cruciale uitkomsten zou leiden.

Rationale van de aanbeveling

De individuele studies rapporteerden vaak gecombineerde uitkomstmaten, waarbij (niet-invasieve) beademing, IC opnameduur, trombotische complicaties, ECMO, nierfunctievervangende therapie en sterfte in verschillende combinaties waren samengenomen. Bij de analyses van de individuele eindpunten bleek het voordeel van therapeutische antistolling onzeker te zijn of onder de van tevoren vastgestelde grens van klinische relevantie te liggen ten opzichte van een profylactische of intermediaire dosis antistolling. Ook bleek het voordeel van een intermediaire dosis antistolling onzeker te zijn of onder de van tevoren vastgestelde grens van klinische relevantie te liggen ten opzichte van een profylactische dosis antistolling. Eerder waren voor de Nederlandse situatie geen grenzen van klinische relevantie vastgesteld voor het instellen van tromboseprofylaxe. De werkgroep heeft zich bij het vaststellen van die grenzen geconformeerd aan de grenzen voor sterfte en IC opname, zoals vastgesteld door de werkgroep voor medicamenteuze behandeling van COVID-19. De grens voor een klinisch relevant verschil in trombotische complicaties werd indirect afgeleid uit de ACCP richtlijn tromboseprofylaxe uit 2012. Uit de onderzochte studies bleek ook dat therapeutische antistolling niet klinisch relevant meer schade berokkende dan een profylactische of intermediaire dosis: het optreden van bloedingen is mogelijk niet klinisch relevant verschillend tussen de groepen. De werkgroep kwam tot de conclusie dat er op grond van de onderzochte studies onvoldoende grond is om een therapeutische of een intermediair profylactische dosis antistolling te adviseren boven een standaard profylactische dosering antistolling voor patiënten met COVID-19 op de intensive care.

Onderbouwing

Achtergrond

Ondanks tromboseprofylaxe en een verbeterde behandeling van COVID-19 komen trombotische complicaties nog frequent voor, met een geschatte incidentie van 23-28% in ICU patiënten en 7-9% in afdelingspatiënten (Jiménez, 2021; Tan, 2021; Nopp, 2021). Het is niet bekend wat de beste dosis van tromboseprofylaxe is (laag, intermediair of therapeutisch). Mede hierdoor verschillen ziekenhuisprotocollen.

Conclusies / Summary of Findings

1. Mortality

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic dose of anticoagulation on mortality when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources:</i> Goligher, 2021; Lemos, 2020.

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on mortality when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source:</i> Sadeghipour, 2021.

2. Length of hospital or ICU stay

Length of hospital stay

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic dose of anticoagulation on length of hospital stay when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources:</i> Lemos, 2020.

Intermediate dose versus standard dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of intermediate dose of prophylactic anticoagulation when compared to standard dose of prophylactic anticoagulation on length of hospital stay in adult COVID-19 patients admitted to the ICU.

Length of ICU stay

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic dose of anticoagulation on length of ICU stay when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources:</i> Lemos, 2020.

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on length of ICU stay when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

3. Organ support

Ventilator-free days

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic dose of anticoagulation on ventilator-free days when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources: Lemos, 2020.</i>

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on ventilator-free days when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

Other organ support free days

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of therapeutic dose of anticoagulation when compared to standard (or intermediate) dose of prophylactic anticoagulation on other organ support free days in adult COVID-19 patients admitted to the ICU.

Intermediate dose versus standard dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of intermediate dose of prophylactic anticoagulation when compared to standard dose of prophylactic anticoagulation on other organ support free days in adult COVID-19 patients admitted to the ICU.

Organ support other than mechanical ventilation

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of therapeutic dose of anticoagulation when compared to standard prophylactic anticoagulation on organ support other than mechanical ventilation in adult COVID-19 patients admitted to the ICU.

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on organ support other than mechanical ventilation when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

4. Venous thromboembolism

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with therapeutic dose of anticoagulation on venous thromboembolism when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Goligher, 2021.</i>

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on venous thromboembolism when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

Thromboembolic complications (VTE/ATE)

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Low GRADE	Treatment with therapeutic dose of anticoagulation may result in a decrease in thromboembolic complications (VTE/ATE) when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources: Goligher, 2021.</i>

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on thromboembolic complications (VTE/ATE) when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

5. Major bleeding

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Low GRADE	Treatment with therapeutic dose of anticoagulation may result in little to no difference in major bleedings when compared to standard (or intermediate) dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Sources: Goligher, 2021; Lemos, 2020; Spyropoulos, 2021.</i>

Intermediate dose versus standard dose of prophylactic anticoagulation

Very low GRADE	The evidence is very uncertain about the effect of treatment with intermediate dose of prophylactic anticoagulation on major bleedings when compared to standard dose of prophylactic anticoagulation in adult COVID-19 patients admitted to the ICU. <i>Source: Sadeghipour, 2021.</i>

6. Heparin induced thrombocytopenia (HIT)

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of therapeutic dose of anticoagulation when compared to standard (or intermediate) dose of prophylactic anticoagulation on HIT in adult COVID-19 patients admitted to the ICU.

Intermediate dose versus standard dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of intermediate dose of prophylactic anticoagulation when compared to standard dose of prophylactic anticoagulation on HIT in adult COVID-19 patients admitted to the ICU.

7. Cumulative transfusion

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of therapeutic dose of anticoagulation when compared to standard prophylactic (or intermediate) dose of anticoagulation on cumulative transfusion in adult COVID-19 patients admitted to the ICU.

Intermediate dose versus standard dose of prophylactic anticoagulation

- GRADE	No studies were found that could answer the question what the effect is of intermediate dose of prophylactic anticoagulation when compared to standard dose of prophylactic anticoagulation on cumulative transfusion in adult COVID-19 patients admitted to the ICU.

Samenvatting literatuur

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Spyropoulos (2021) describes a multicenter open label randomized clinical trial evaluating the effects of therapeutic-dose low-molecular-weight heparin vs institutional standard or intermediate prophylactic dose heparins for thromboprophylaxis in high-risk hospitalized patients with COVID-19. Patients were enrolled from March 8, 2020, through May 14, 2021, at 12 centers in the US. A total of 11649 patients were assessed for eligibility. Eligible patients consisted of hospitalized nonpregnant adults 18 years or older with COVID-19 diagnosed by nasal swab or serologic testing. Moreover, there was a requirement for supplemental oxygen per investigator judgment and a plasma D-dimer level greater than 4 times the upper limit of normal based on local laboratory criteria or a sepsis-induced coagulopathy score of 4 or greater. 257 patients were randomized into the therapeutic heparin dose group (n= 130) or standard/intermediate prophylactic heparin dose group (n = 127). 45 out of 129 patients in the therapeutic dose group were admitted to the ICU, versus 38 out of 124 in the standard prophylactic dose group. Treatment began after randomization and was stopped at hospital discharge or upon occurrence of a primary efficacy outcome, key secondary outcome, or principal safety outcome requiring study drug discontinuation. All patients without a primary or key secondary outcome event underwent lower extremity Doppler compression ultrasonography at hospital day 10 + 4 or at discharge if sooner. The length of follow-up was 30 ±2 days after randomization. For the primary efficacy outcome (venous thromboembolism, arterial thromboembolism or death) and major bleeding, patients were stratified based on intensive care unit (ICU) or non-ICU status. For all other outcomes, no stratification was performed. Patients in the therapeutic dose group had a mean age of 65.8 years (SD 13.9) versus 67.7 years (SD 14.1) in the standard prophylactic dose group and the small majority was male (52.7% in the intervention versus 54.8% in the control group). The study groups were comparable with respect to baseline characteristics.

Goligher (2021) describes an open-label, adaptive, multiplatform RCT (mpRCT). In this mpRCT, three platforms (REMAPCAP, ATTACC and ACTIV-4a) were integrated to evaluate therapeutic dose anticoagulation versus usual-care pharmacologic thromboprophylaxis in critically ill patients with COVID-19. Patients were recruited from different countries, e.g. the United Kingdom, United States, Canada, Brazil. Patients were

included in the mpRCT if they had a laboratory confirmed COVID-19 infection, they had severe COVID-19 (which was defined as COVID-19 that led to receipt of ICU-level respiratory or cardiovascular organ support in an ICU). A total of 1207 patients underwent randomization at 393 sites in 10 countries, until the pre-specified criterion for futility had been met. Patients were randomized to receive therapeutic dose anticoagulation with heparin (n=591) or usual-case thromboprophylaxis (n=616). After exclusion, 534 patients in the therapeutic dose group and 564 patients in the usual-care group were included in the primary analysis. The mean age of patients in the therapeutic dose group was 60.4 years (SD 13.1) versus 61.7 years (SD 12.5) in the usual-care group. The majority in both groups was male: 387 patients (72.2%) in the therapeutic dose group, versus 385 patients (67.9%) in the usual-care group. The study groups were comparable with respect to baseline characteristics.

Lemos (2020) describes a randomized, controlled, open-label, single-center, phase II study conducted in Brazil, evaluating therapeutic dose enoxaparin versus standard anticoagulant thromboprophylaxis in COVID-19 patients requiring mechanical ventilation. Adult patients (>18 years of age) were included in this study if they suffered from respiratory failure requiring mechanical ventilation and laboratory confirmed SARS-CoV-2 infection. Twenty patients were randomized to receive therapeutic enoxaparin (n=10) or prophylactic anticoagulation (UFH and LMWH, n=10). All patients who were randomized were included in the primary analysis. The mean age of patients in the therapeutic dose group was 55 years (SD 10) versus 58 years (SD 16) in the prophylactic dose group. The majority was male: nine out of ten patients in the therapeutic dose group, versus seven out of ten patients in the prophylactic dose group. The study groups were comparable with respect to baseline characteristics.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) describes a multicenter open-label randomized clinical trial (INSPIRATION trial) comparing intermediate versus standard dose of prophylactic anticoagulation in adult patients with COVID-19 admitted to the ICU. Patients were recruited between July 29, 2020, and November 19, 2020, conducted in Iran at 10 academic centers in Tehran and Tabriz. Patients were eligible if they were admitted to the ICU with polymerase chain reaction testing–confirmed COVID-19 within 7 days of the index hospitalization. Patients were excluded when their life expectancy was less than 24 hours. Also, patients with an established indication for therapeutic-dose anticoagulation, weight less than 40 kg, pregnancy, history of heparin-induced thrombocytopenia, platelet count less than $50 \times 10^3 / \mu\text{L}$, or overt bleeding were excluded. A total of 600 patients were randomized into the intermediate prophylactic dose group (n=299) or the standard dose prophylactic anticoagulation group (n=299). The primary anticoagulant agent in both groups was enoxaparin. In case a patient had severe kidney insufficiency, an unfractionated heparin was used. Treatments were continued until 30 days of follow-up, irrespective of hospital discharge status. Ultimately, 562 patients were included in the prespecified primary analysis. The median age of patients in the intermediate prophylactic dose group (n=276) was 62 years (IQR 51 to 70.7), versus 61 years (IQR 47 to 71) in the standard prophylactic dose group (n=286). The majority in both groups was male: 162 patients (58.7%) in the intermediate prophylactic dose group, versus 163 patients (57.0%) in the standard prophylactic dose group. Except for history of cigarette smoking, which was more frequent in the intermediate prophylactic dose group, the study groups were comparable with respect to baseline characteristics.

Bikdeli (2021) reports the final 90-day follow-up results of the INSPIRATION trial by **Sadeghipour (2021)**.

Therefore, the study design and included patients were the same as described above. The number of patients included in the primary analysis were not altered (n=276 in the intermediate prophylactic dose group versus n=286 in the standard prophylactic dose group). These articles are therefore taken together for the literature analysis.

Table 2. Overview of included RCTs that compared therapeutic dose anticoagulation with standard (or intermediate) dose anticoagulation and intermediate dose anticoagulation with standard dose anticoagulation in COVID-19 patients admitted to the ICU

<i>Author, year and trial name</i>	<i>Intervention (I) and control (C)</i>	<i>Sample size for analysis</i>	<i>Doses</i>	<i>Duration</i>
<u>Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation</u>				
Spyropoulos, 2021 HEP-COVID Randomized Clinical Trial	I: therapeutic-dose low-molecular-weight heparin (enoxaparin) C: institutional standard prophylactic or intermediate-dose heparins for thromboprophylaxis	I: N= 45 ICU admitted patients C: N= 38 ICU admitted patients Total = 83	I: 1 mg/kg subcutaneously twice daily if CrCl was 30 mL/min/1.73 m ² or greater or 0.5 mg/kg twice daily if CrCl was 15-29 mL/min/ 1.73 m ² C: could include unfractionated heparin (UFH), up to 22 500 IU subcutaneously (divided twice or thrice daily); enoxaparin, 30 mg or 40 mg subcutaneously once or twice daily (weight based enoxaparin 0.5 mg/kg subcutaneously twice daily was permitted but strongly discouraged); or dalteparin, 2500 IU or 5000 IU subcutaneously daily	Study drug was administered for the duration of hospitalization, including patient transfers to ICU settings.

Goligher, 2021 The REMAP-CAP, ACTIV-4a, and ATTACC Investigators	I: therapeutic-dose anticoagulation with heparin C: pharmacologic thromboprophylaxis in accordance with local usual care	I: N= 534 C: N= 564 Total = 1098	I: Therapeutic-dose anticoagulation was administered according to local site protocols for the treatment of acute venous thromboembolism C: Usual-care thromboprophylaxis was administered at a dose and duration determined by the treating clinician according to local practice, which included either standard low-dose thromboprophylaxis or enhanced intermediate-dose thromboprophylaxis. The anticoagulation and thromboprophylaxis regimens that were specified by each platform are detailed in the Supplementary Appendix (page 49-51 and Table S1 at page 65).	I: Up to 14 days or until recovery (defined as either hospital discharge or discontinuation of supplemental oxygen for at least 24 hours). C: Up to 14 days or hospital discharge, whichever comes first. After this period, decisions regarding thromboprophylaxis are at discretion of treating clinician The trial was stopped when the prespecified criterion for futility was met for therapeutic-dose anticoagulation.

Lemos, 2020 HESACOVID trial	I: therapeutic enoxaparin C: standard anticoagulant thromboprophylaxis	I: N= 10 C: N= 10 Total = 20	I: subcutaneous (SC) enoxaparin with the dose according to age and adjusted daily by the creatinine clearance (CrCl) estimated by the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation. See article for exact doses per age group. C: subcutaneous unfractionated heparin (UFH) at a dose of 5000 IU TID (if weight < 120 kg) and 7500 IU TID (if weight > 120 kg) or enoxaparin at a dose of 40 mg OD (if weight < 120 kg) and 40 mg BID (if weight > 120 Kg) according to the doctor's judgment.	I: The median of the therapeutic enoxaparin treatment duration was 14 days, ranging from 9 to 14 days C: ?
Intermediate dose versus standard dose of prophylactic anticoagulation				
INSPIRATION trial <u>Sadeghipour, 2021</u> (initial study) <u>Bikdeli, 2021</u> (extension of initial study/follow-up measurements at day 90)	I: intermediate-dose enoxaparin C: standard prophylactic anticoagulation enoxaparin	I: N= 276 C: N= 286 Total = 562	I: 1 mg/kg daily, with modification according to body weight and creatinine clearance. C: 40 mg daily, with modification according to body weight and creatinine clearance.	Irrespectively of hospital discharge status, the assigned treatments were planned to be continued until the 30-day follow-up (Sadeghipour, 2021) or 90-day follow-up (Bikdeli, 2021).

Table 3. Overview of composite outcomes and results per study

Study	Primary composite outcome	Results
INSPIRATION trial 1. Sadeghipour, 2021 (30 days) 2. Bikdeli, 2021 (90 days)	Composite of adjudicated acute venous thromboembolism, arterial thrombosis, treatment with extracorporeal membrane oxygenation, or all-cause mortality.	1. Intermediate prophylactic dose group: 126 out of 276 (45.7%) patients Standard prophylactic dose group: 126 out of 286 (44.1%) patients 2. Intermediate prophylactic dose group: 132 out of 276 (47.8%) patients Standard prophylactic dose group: 130 out of 286 (45.4%) patients
Goligher, 2021 Multiplatform trial	Median number of days free of cardiovascular or respiratory organ support. This was evaluated on an ordinal scale that combined in-hospital death and the number of organ support free days up to day 21 among patients who survived to hospital discharge. If a patient died, they were assigned a value of -1.	In the therapeutic dose group, the median number of organ support-free days was 1 day (IQR -1 to 16), versus 4 days (IQR -1 to 16) in the standard prophylactic dose group.
Spyropoulos, 2021 HEP-COVID trial	Composite outcome: VTE, ATE, or death Measured in the ICU-stratum	Therapeutic dose group: 23 out of 45 (51.1%) patients Standard prophylactic dose group: 21 out of 38 (55.3%) patients

Results

1. Mortality

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) reported death in hospital. A total of 199 out of 534 (37.3%) patients died in the therapeutic dose group, versus 200 out of 564 (35.5%) in the standard prophylactic dose group. The risk difference (RD) was 1.8% in favor of the standard prophylactic dose group (95%CI -3.9% to 7.5%). The corresponding NNT was 56. This was not considered to be a clinically relevant difference.

Lemos (2020) reported in-hospital mortality. A total of 2 out of 10 (20.0%) patients died in the therapeutic dose group, versus 5 out of 10 (50.0%) in the standard prophylactic dose group. The RD was 30.0% in favor of the therapeutic dose group (95%CI -69.7% to 9.7%). The corresponding NNT was 3. This was considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure *mortality* was downgraded from high to **very low** because in Goligher (2021) some patients are missing from the analyses and it is not clear why, and many patients were excluded after randomization in both groups (risk of bias, -1), and the confidence interval around the RD crossing the upper and lower thresholds for clinical relevance (imprecision, -2). Lemos (2020) was given few weight in the determination of the level of evidence, because of the very small study population.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) reported all-cause mortality at day 30. In the intermediate prophylactic dose group, 119 out of 276 (43.1%) patients died, versus 117 out of 286 (40.9%) patients in the standard prophylactic dose group. The RD was 2.2% in favor of the standard prophylactic dose group (95%CI -6.0% to 10.4%). The corresponding NNT was 45. This was not considered to be a clinically relevant difference.

At day 90, Bikdeli (2021) reported that 127 out of 276 (46.0%) patients died, versus 123 out of 286 (43.0%) patients in the standard prophylactic dose group.

Level of evidence

The level of evidence regarding the outcome measure *mortality* was downgraded from high to **very low** because of the study population differing from what was defined in the PICO (indirectness, -1), the confidence interval around the RD crossing the upper and lower thresholds for clinical relevance (imprecision, -2). The level of evidence is based on the results reported in Sadeghipour (2021).

2. Length of hospital or ICU stay

Length of hospital stay

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Lemos (2020) reported the median length of hospital stay. The median length of hospital stay was 31 days (IQR 22 to 35) in the therapeutic dose group, versus 30 days (IQR 23 to 38) in the standard prophylactic dose group. The difference in median days was 1 day. This was not considered to be a clinically relevant difference.

Goligher (2021) did not report length of hospital stay.

Level of evidence

The level of evidence regarding the outcome measure *length of hospital stay* was downgraded from high to **very low** because of the small sample size and wide interquartile range (imprecision, -3).

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) did not report length of hospital stay.

Length of ICU stay

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Lemos (2020) also reported the median number of ICU-free days. This was 12 days (IQR 2 to 12) in the therapeutic dose group, versus 0 days (IQR 0 to 10) in the standard prophylactic dose group.

Goligher (2021) did not report length of ICU stay.

Level of evidence

The level of evidence regarding the outcome measure *length of ICU stay* was downgraded from high to **very low** because of the outcome measure not being the same as defined in the PICO (indirectness, -1), and the small sample size and wide interquartile range (imprecision, -2).

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) reported the median length of ICU stay. The median length of ICU stay for the intermediate prophylactic dose group was 5 days (IQR 2 to 10), versus 6 days (IQR 3 to 11) in the standard prophylactic dose group. The difference in median days was 1 day. This was not considered to be a clinically relevant difference.

Sadeghipour (2021) also reported the number of patients discharged from the ICU. The number of patients discharged from the ICU in the intermediate prophylactic dose group was 169 out of 276 (61.2%), versus 174 out of 286 (60.8%) in the standard prophylactic dose group.

Bikdeli (2021) did not report length of ICU stay at day 90.

Level of evidence

The level of evidence regarding the outcome measure *length of ICU stay* was downgraded from high to **very low** because of the study population differing from what was defined in the PICO (indirectness, -1), and the wide interquartile range in both groups (imprecision, -2).

3. Organ support free days

Ventilator-free days

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Lemos (2020) reported the median number of ventilator-free days. In the therapeutic dose group, the median number of ventilator-free days was 15 days (IQR 6 to 16), versus 0 days (IQR 0 to 11) in the standard prophylactic dose group.

Goligher (2021) did not report ventilator-free days.

Level of evidence

The level of evidence regarding the outcome measure *ventilator-free days* was downgraded from high to **very low** because of the small sample size and the wide interquartile range in both groups (imprecision, -3).

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) reported the median number of ventilator-free days. In the intermediate prophylactic dose group, the median number of ventilator-free days was 30 days (IQR 3 to 30), versus 30 days (IQR 1 to 30) in the standard prophylactic dose group. The difference in median days was zero days. This was not considered to be a clinically relevant difference.

Bikdeli (2021) did not report ventilator-free days at day 90.

Level of evidence

The level of evidence regarding the outcome measure *ventilator-free days* was downgraded from high to **very low** because of the study population differing from what was defined in the PICO (indirectness, -1), and the wide interquartile range in both groups (imprecision, -2).

Other organ support free days

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) and Lemos (2020) did not report on other organ support free days.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) did not report on other organ support free days.

Organ support other than mechanical ventilation

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) and Lemos (2020) did not report on other organ support than mechanical ventilation.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) reported extracorporeal membrane oxygenation (ECMO) as part of the primary composite outcome (see Table 2), but not on its own. In addition, Sadeghipour (2021) reported new in-hospital kidney replacement therapy. In the intermediate prophylactic dose group, 10 out of 276 (3.6%) patients needed kidney replacement therapy, versus 7 out of 286 (2.4%) patients in the standard prophylactic dose group. The difference was 1.2% in favor of the standard prophylactic dose group (95%CI -1.7% to 4.0%). This was not considered to be a clinically relevant difference. Bikdeli (2021) reported the same numbers at day 90.

Level of evidence

The level of evidence regarding the outcome measure *organ support other than mechanical ventilation* was downgraded from high to **very low** because of the study population differing from what was defined in the PICO (indirectness, -1), and the low number of events (imprecision, -2).

4. Venous thromboembolism

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) and Lemos (2020) did not report the number of patients with VTE.

However, Goligher (2021) did report the number of **events** for deep venous thrombosis and pulmonary embolism separately. In the therapeutic dose group 6 events for deep venous thrombosis were reported, versus 6 events in the standard prophylactic dose group. For pulmonary embolism, 13 events were reported in the therapeutic dose group, versus 42 events in the standard prophylactic dose group.

Level of evidence

The level of evidence regarding the outcome measure *venous thromboembolism* was downgraded from high to **very low** because in Goligher (2021) some patients are missing from the analyses and it is not clear why, and many patients were excluded after randomization in both groups (risk of bias, -1), indirectness in the outcome measure (indirectness, -1), the low number of events (imprecision, -1).

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) reported adjudicated venous thromboembolism at day 30. In the intermediate prophylactic dose group 9 out of 276 patients (3.3%) developed adjudicated venous thromboembolism, versus 10 out of 286 (3.5%) in the standard prophylactic dose group. The RD was 0.24% in favor of the intermediate prophylactic dose group (95%CI -3.2% to 2.8%). The NNT was 417. This was not considered to be a clinically relevant difference.

Bikdeli (2021) reported the same outcome in the same patients at day 90. No differences occurred in the incidence between day 30 and 90.

Level of evidence

The level of evidence regarding the outcome measure *venous thromboembolism* was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), the study population differing from what was defined in the PICO (indirectness, -1), and the confidence interval around the RD crossing the lower threshold for clinical relevance (imprecision, -1).

Thromboembolic complications (VTE/ATE)

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) reported the number of patients with any thrombotic event (defined as pulmonary embolism, myocardial infarction, ischemic cerebrovascular event, systemic arterial thromboembolism): 38 out of 530 patients (7.2%) experienced a thrombotic event in the therapeutic dose group, versus 62 out of 559 patients (11.1%) in the standard prophylactic dose group. The RD was 3.9% in favor of the therapeutic dose group (95%CI -7.3% to 0.5%). The corresponding NNT was 26. This was considered to be a clinically relevant difference.

Lemos (2020) reported the number of patients with thrombotic events: 2 out of 10 (2.0%) patients experienced a thrombotic event in the therapeutic dose group, versus 2 out of 10 (2.0%) patients in the standard prophylactic dose group. The RD was 0.0% (95%CI -35.1% to 35.1%). This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure *thromboembolic complications* was downgraded from high to **low** because in Goligher (2021) some patients are missing from the analyses and it is not clear why, and many patients were excluded after randomization in both groups (risk of bias, -1), and the confidence interval around the RD crossing the lower threshold for clinical relevance (imprecision, -1). Lemos (2020) was given no weight in the determination of the level of evidence, because of the very small study population.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) did not report the number of patients with thromboembolic events (VTE/ATE).

However, Sadeghipour (2021) reported the number of patients with acute peripheral arterial thrombosis, ischemic stroke, and type I acute myocardial infarction, all three objectively clinically diagnosed. None of the 276 patients in the intermediate prophylactic dose group and none of the 286 patients in the standard prophylactic dose group were diagnosed with acute peripheral arterial thrombosis and/or type I acute myocardial infarction. In the intermediate prophylactic dose group, 1 out of 276 (0.4%) patients developed ischemic stroke, versus 1 out of 286 (0.3%) patients in the standard prophylactic dose group.

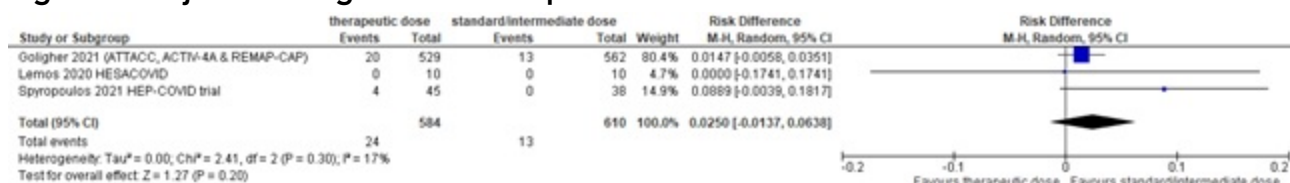
Level of evidence

The level of evidence regarding the outcome measure *thromboembolic complications* was downgraded from high to **very low** because of the open-label study design (risk of bias, -1), indirectness in the outcome measure and study population (indirectness, -1), and the low number of events (imprecision, -1).

5. Major bleeding

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Figure 1: Major bleeding in COVID-19 patients admitted to the ICU



Z: p-value of overall effect; df: degrees of freedom; I²: statistical heterogeneity; CI: confidence interval

A total of 24 out of 584 (4.1%) patients developed a major bleeding in the therapeutic dose group, versus 13 out of 610 (2.1%) in the standard/intermediate prophylactic dose group. The pooled risk difference (RD) was 2.5% in favor of the standard/intermediate prophylactic dose group (95%CI -1.4% to 6.4%; figure 1). The

corresponding NNH was 40. This was not considered to be a clinically relevant difference.

Level of evidence

The level of evidence regarding the outcome measure *major bleeding* was downgraded from high to **low** because in Goligher (2021) some patients are missing from the analyses and it is not clear why, and many patients were excluded after randomization in both groups (risk of bias, -1), and the confidence interval around the RD crossing the upper threshold for clinical relevance (imprecision, -1).

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) reported major bleeding. In the intermediate prophylactic dose group 7 out of 276 (2.5%) patients developed a major bleeding, versus 4 out of 286 (1.4%) patients in the standard prophylactic dose group. The RD was 1.14% in favor of the standard prophylactic dose group (95%CI -1.16% to 3.44%). The corresponding NNH was 88. This was not considered to be a clinically relevant difference. Bikdeli (2021) reports the same numbers at day 90.

Level of evidence

The level of evidence regarding the outcome measure *major bleeding* was downgraded from high to **very low** because of the open-label study designs (risk of bias, -1), the study population differing from what was defined in the PICO (indirectness, -1), and the confidence interval around the RD crossing the upper threshold for clinical relevance (imprecision, -1).

6. Heparin induced thrombocytopenia (HIT)

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) and Lemos (2020) did not report HIT.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) did not report HIT.

7. Cumulative transfusion

Therapeutic dose versus standard (or intermediate) dose of prophylactic anticoagulation

Goligher (2021) and Lemos (2020) did not report cumulative transfusion.

Intermediate dose versus standard dose of prophylactic anticoagulation

Sadeghipour (2021) and Bikdeli (2021) did not report cumulative transfusion.

However, Sadeghipour (2021) reported a sub-category of major bleeding: 'BARC Type 3a- hemoglobin drop of 3 to 5 g/dL or any transfusion'. In the intermediate prophylactic dose group, 3 out of 276 (1.1%) patients reported this outcome, versus 4 out of 286 (1.4%) patients in the standard prophylactic dose group. Bikdeli (2021) reported the same numbers at day 90.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the efficacy and safety of anticoagulation therapy in COVID-19 patients at the ICU?

PICO 1

P: all adult COVID-19 patients admitted to the ICU who are not already on chronic therapeutic anticoagulants

I: therapeutic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

C: standard or intermediate prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) or no use of standard or intermediate prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

O: mortality, major bleeding, venous thromboembolism, thromboembolic complications, length of hospital or ICU stay, organ support (ventilator-free days, other organ support free days, and organ support other than mechanical ventilation), heparin induced thrombocytopenia, and cumulative transfusion

PICO 2

P: all adult COVID-19 patients admitted to the ICU who are not already on chronic therapeutic anticoagulants

I: intermediate prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

C: standard prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) or no use of standard or intermediate prophylactic dose (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)

O: mortality, major bleeding, venous thromboembolism, thromboembolic complications, length of hospital or ICU stay, organ support (ventilator-free days, other organ support free days, and organ support other than mechanical ventilation), heparin induced thrombocytopenia, and cumulative transfusion

We searched for standard dose of prophylaxis and intermediate dose of prophylaxis; the latter is typically a doubling of the standard dose of prophylaxis. We also searched for a therapeutic dose of prophylaxis (intensive dose of prophylaxis; referred to as *therapeutic dose*). For aspirin only one dose (80-100 mg per day) was searched.

Relevant outcome measures

The guideline development group considered mortality, ventilator-free days, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined) and major bleeding as critical outcome measures for decision making; and length of hospital or ICU stay, other organ support free days, organ support other than mechanical ventilation, heparin induced thrombocytopenia, and cumulative transfusion as important outcome measures for decision making.

The working group defined a risk difference of 3% as a minimal clinically (patient) important difference for mortality, venous thromboembolism, thromboembolic complications (venous and arterial thrombotic complications combined) and major bleeding; 3 days for length of hospital(/ICU) stay, ventilator-free days,

and other organ support free days; a risk difference of 5% for organ support other than mechanical ventilation (yes/no), an absolute risk difference of 0.5 % for heparin induced thrombocytopenia; and an absolute risk difference of 10% for cumulative transfusion.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until October 18th 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 686 hits. Studies were selected based on the following criteria:

- randomized controlled trial (RCT)
- peer reviewed and published in indexed journal or pre-published
- comparing treatment with
 1. a therapeutic dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) with a prophylactic dose or no dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)
 2. an intermediate prophylactic dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin) with a standard prophylactic dose or no dose of anticoagulant (low molecular weight heparin, unfractionated heparin, direct oral anticoagulants, vitamin K-antagonists, aspirin)
- in critically ill patients with COVID-19 admitted to the ICU.

Fourteen studies were initially selected based on title and abstract screening. After reading the full text, nine studies were excluded (see the table with reasons for exclusion under the tab Methods), and five studies were included.

Results

Five studies were included in the analysis of the literature. Three studies investigated a therapeutic dose anticoagulant versus standard (or intermediate) prophylactic dose anticoagulant in COVID-19 patients admitted to the ICU (PICO 1). One study (for which different follow-up times – day 30 and day 90 – are described in two articles) investigated an intermediate prophylactic dose anticoagulant versus standard prophylactic dose anticoagulant in COVID-19 patients admitted to the ICU (PICO 2). No subgroups were made based on the type of anticoagulant used, as all studies used a heparin. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 14-04-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Niet-invasieve ademhalingsondersteuning

Waar gaan deze richtlijnmodules over?

Deze richtlijnmodules behandelen de indicaties en randvoorwaarden voor niet-invasieve ademhalingsondersteuning bij patiënten met COVID-19 op de intensive care of verpleegafdeling.

Voor wie zijn deze richtlijnmodules bedoeld?

Deze richtlijnmodules zijn bedoeld voor ieder zorgprofessionals die betrokken zijn bij niet-invasieve ademhalingsondersteuning van patiënten met COVID-19 die opgenomen zijn op de verpleegafdeling of de IC.

Voor patiënten

Als de artsen zien dat u te weinig zuurstof in uw bloed heeft, kunt u extra zuurstof krijgen. Dit is dezelfde zuurstof die u thuis kunt krijgen, maar in het ziekenhuis kan meer zuurstof worden gegeven. Meestal voelt u zich hierdoor ook minder benauwd.

- U kunt extra zuurstof krijgen op verschillende manieren:
- via een slangetje in uw neus
- via een kapje op uw gezicht
- via een speciaal apparaat via een slangetje in uw neus. Hiermee kan veel zuurstof in 1 keer gegeven worden.

U ademt bij deze behandelingen zelf. Via het slangetje of kapje wordt er extra zuurstof en lucht in uw longen geblazen. Hierdoor kunt u beter ademen en blijft er genoeg zuurstof in uw bloed.

Zie ook de informatie op [Thuisarts.nl](https://www.thuisarts.nl):

<https://www.thuisarts.nl/corona-in-ziekenhuis/ik-heb-corona-en-krijg-behandeling-in-ziekenhuis>

Hoe is de richtlijnmodule tot stand gekomen?

Op initiatief van de Federatie Medisch Specialisten is begin 2021 gestart met de ontwikkeling van de richtlijn COVID-19. Deze richtlijn beschrijft de infectiepreventie, diagnostiek, behandeling en revalidatie en nazorg voor alle COVID-19 (verdachte) patiënten. Deze richtlijn is deels gebaseerd op eerder gepubliceerde leidraden over COVID-19. In het voorjaar van 2020 is de leidraad 'niet-invasieve ademhalingsondersteuning bij acute respiratoire insufficiëntie bij COVID-19' ontwikkeld op initiatief van de Nederlandse Vereniging van Artsen voor Longziekten en Tuberculose (NVALT). Deze leidraad is geüpdatet en doorontwikkeld tot een richtlijnmodule met 2 deelvragen. Hiervoor is in 2020 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen die betrokken zijn bij behandeling van respiratoir insufficiënte patiënten met COVID-19 die behandeld zouden kunnen worden niet-invasieve ademhalingsondersteuning. Daarnaast is er aandacht besteed aan het patiëntenperspectief door de module voor commentaar voor te leggen aan de Patiëntenfederatie Nederland. De eventueel aangeleverde commentaren zijn bekeken en verwerkt.

Status van de richtlijn

Gedurende de pandemie zijn diverse leidraden gepubliceerd. Voor onderwerpen die momenteel (nog) niet als modules zijn gepubliceerd, verwijzen we u naar de website:

<https://www.demedischspecialist.nl/onderwerp/details/richtlijnen-handreikingen-leidraden>.

Niet-invasieve ademhalingsondersteuning bij acute respiratoire insufficiëntie bij COVID-19

Uitgangsvraag

Wanneer is het gebruik van high flow nasal cannula (HFNO) effectief bij patiënten met acuut hypoxemisch respiratoire falen ten gevolge van COVID-19?

De uitgangsvraag bevat de volgende deelvragen:

- Wanneer is HFNO bij patiënten met acuut hypoxemisch respiratoir falen ten gevolge van COVID-19 verantwoord te gebruiken in plaats van direct te starten met invasieve beademing?
- Wanneer is HFNO bij patiënten met acuut hypoxemisch respiratoir falen ten gevolge van COVID-19 van meerwaarde vergeleken met conventionele zuurstoftherapie?

Wanneer is het gebruik van continuous positive airway pressure (CPAP) effectief bij patiënten met acuut hypoxemisch respiratoir falen ten gevolge van COVID-19?

De uitgangsvraag bevat de volgende deelvragen:

- Wanneer is CPAP bij patiënten met acuut hypoxemisch respiratoir falen ten gevolge van COVID-19 verantwoord te gebruiken in plaats van direct te starten met invasieve beademing?
- Wanneer is CPAP bij patiënten met acuut hypoxemisch respiratoir falen ten gevolge van COVID-19 van meerwaarde vergeleken met conventionele zuurstoftherapie?

Aanbeveling

Overweeg, in overleg met de patiënt, te starten met HFNO of CPAP bij COVID-19 patiënten met acuut hypoxemisch respiratoir falen, bij wie niet direct invasieve beademing nodig is.

Overweeg een intensivist te consulteren bij patiënten met een wel-invasief beademen beleid voor overleg omtrent vervolgbesluit indien ondanks inzet van HFNO met een flow van 60L/min en een FiO₂ van ≥60% of CPAP met PEEP ≥10 cm H₂O en een FiO₂ van ≥60% er sprake is van:

- PaO₂ <8 kPa (60 mmHg) of een perifere saturatie <92%; óf
- tachypneu >30/min; óf
- gebruik van hulpademhalingspijpen.

Bij patiënten met COVID-19 en een behandeling gericht op comfort en niet op genezing heeft (niet-)invasieve ademhalingsondersteuning geen plaats.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Hoewel het literatuuronderzoek ten aanzien van HFNO en CPAP ten opzichte van COT en IMV apart is gedaan laten de overwegingen zich samennemen. De kwaliteit van het bewijs is voor alle uitkomstmaten zeer laag of afwezig. Ten aanzien van het gebruik van CPAP zijn in het geheel geen vergelijkende studies van voldoende kwaliteit gevonden. Hier ligt een belangrijke kennislacune. De aanbevelingen zullen daarom gebaseerd worden op andere overwegingen waaronder expert opinie, waar mogelijk onderbouwd met (indirecte) literatuur.

Patiënten met hypoxemisch respiratoir falen als gevolg van COVID-19 hebben mogelijk baat bij HFNO of CPAP omdat:

- bij hoge flow, kamerlucht nauwelijks wordt bijgemengd bij de inspiratie, wat het aanbod van FiO_2 hoger maakt;
- de CO_2 uitwas in de hogere luchtwegen wordt verbeterd;
- de hoge flow de luchtwegweerstand verlaagt (Spoletini, 2015).

Dit kan leiden tot verminderde ademarheid en verbetert de ademhalings efficiëntie.

CPAP voegt daar positieve eind-expiratoire druk aan toe met als gevolg alveolaire recruitment tijdens expiratie waardoor verbeterde oxygenatie. Vanwege deze positieve effecten op oxygenatie en ademarheid worden HFNO en CPAP ingezet bij hypoxemisch respiratoir falen.

Zowel het gebruik van HFNO als CPAP heeft als mogelijk nadeel dat endotracheale intubatie wellicht wordt uitgesteld (Esquinas, 2014; Gorman, 2021). De hoge ademarheid die patiënten leveren bij niet-invasieve ademhalingsondersteuning kan leiden tot grote pleurale drukwisselingen, met mogelijk longschade tot gevolg: patiënt self-inflicted lung injury (P-SILI) (Brochard, 2017). In de literatuur is het aanwezig zijn van P-SILI bij COVID-19 een punt van discussie (Gattinoni, 2021; Tobin, 2020; Tobin, 2020). De studie van Mellado-Artigas (2021) is uit dat oogpunt interessant. Deze multicenter observationele studie waarin patiënten met vroege intubatie (<24 uur ICU opname) werden vergeleken met patiënten die initieel behandeld werden met HFNO laat zien dat, na propensity matching (N=61 per groep), het aantal ventilator-free days (VFDs) op dag 28 hoger was en de IC opname duur korter in de HFNO-groep. Vergelijken van patiënten die vroeg versus later geïntubeerd werden toonde geen verschil in VFDs, ICU-opnameduur of mortaliteit.

In nog niet peer-reviewed onderzoek van de RECOVERY-RS onderzoeksgroep (Perkins, 2021) worden HFNO en CPAP vergeleken met COT. Patiënten worden in deze studie gerandomiseerd tussen deze drie vormen van zuurstoftherapie. De primaire (gecombineerde) uitkomstmaat was intubatie of mortaliteit binnen 30 dagen. Deze randomized clinical trial is voortijdig gestopt vanwege afnemende patiënten aantallen en aflopen van de subsidie-periode. In totaal zijn 1273 patiënten geïnccludeerd (n= 380 CPAP, n=418 HFNO en n=475 COT). Het verschil in intubatie en mortaliteit binnen 30 dagen is significant in het voordeel van CPAP ten opzichte van COT. Tussen HFNO en COT is geen verschil gevonden. Belangrijke kanttekeningen bij deze RCT is dat de trial mogelijk underpowered was, er veel cross-over tussen de groepen waren, en de uitvoering van de interventies summier beschreven is, wat interpretatie en generaliseerbaarheid bemoeilijkt.

In de 'Australian Guideline for the clinical care of people with COVID-19' wordt aanbevolen om bij patiënten die met COT hun saturatie niet tussen de 92-96% kunnen houden, CPAP met PEEP tussen 10-12cmH₂O te

overwegen. HFNO wordt geadviseerd als alternatief wanneer CPAP niet wordt getolereerd. Frequentie monitoring wordt ook hier benoemd, evenals het niet uitstellen van intubatie bij respiratoire verslechtering zonder hieraan specifieke parameters mee te geven.

Op basis van de kennis van de fysiologie en bovenstaande studies en guidelines is onvoldoende reden om aan te nemen dat patiënten met hypoxemisch respiratoir falen ten gevolge van COVID-19 meer risico lopen op P-SILI als endotracheale intubatie wordt uitgesteld tot niet-invasieve ondersteuning faalt. Er lijkt een klein voordeel voor het gebruik van CPAP en HFNO boven COT maar de beperkte studies zijn daarover niet eensluidend. En juist vroege intubatie lijkt te leiden tot meer intubaties en langere IC-opnameduur. Zie ook de module invasieve beademing bij COVID-19 (in ontwikkeling).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Indien voor een patiënt zowel CPAP als HFNO beschikbaar zijn, dan verdient het de voorkeur om een keuze te maken in overleg met de patiënt. Beide modaliteiten kunnen evt. afgewisseld worden. Opvallende kanttekening is, dat in de literatuur is beschreven, dat CPAP middels een helm door patiënten beter wordt verdragen dan CPAP via een masker, daarnaast geeft een helm minder lekkage en een betere passing (waardoor minder decubitus) (Ferreyro, 2020).

Endotracheale intubatie met diepe sedatie heeft grote gevolgen voor de patiënt. De patiënt verliest de mogelijkheid tot communicatie en dus ook de mogelijkheid om behandelwensen kenbaar te maken aan familie en professionals. Het proces van ontwennen van invasieve beademing is voor veel patiënten zeer belastend en soms zelfs traumatisch. Dit zijn vanuit patiëntperspectief belangrijke argumenten om endotracheale intubatie zo lang mogelijk uit te stellen. Daar tegenover staat dat voor patiënten met ernstige dyspneu-sensatie, of discomfort gerelateerd aan COVID-19, intubatie juist als positief kan worden ervaren.

Kosten (middelenbeslag)

COT is een relatief goedkope manier van zuurstoftoediening. De middelen en materialen hiervoor zijn in ziekenhuizen ruimschoots aanwezig evenals benodigde kennis bij zowel artsen als verpleegkundigen. Wanneer CPAP/optiflow vergeleken wordt met COT, dan zijn de kosten hoger. Dit hangt samen met de gebruikte disposables en met het feit dat optiflow en CPAP meer arbeidsintensief zijn dan COT. Invasieve mechanische ventilatie is een medische behandeling voor patiënten met ernstig COVID-19 gerelateerde hypoxemie. Deze behandeling wordt alleen toegepast op een intensive care afdeling. In tegenstelling tot COT zijn de kosten hiervoor hoog. Vanuit sociaal-economisch perspectief heeft behandeling met niet-invasieve respiratoire ondersteuning voor patiënten met COVID-19 en hypoxemisch falen de voorkeur. Vroege endotracheale intubatie, waarbij risico bestaat dat patiënten invasief beademd worden die dit uiteindelijk niet nodig blijken te hebben, leidt tot onnodige belasting van financiële middelen en andere resources. De inzet van HFNO en CPAP kan deze kosten verlagen.

Aanvaardbaarheid, haalbaarheid en implementatie

Zowel HFNO als CPAP kunnen potentieel worden ingezet op zowel de verpleegafdeling als de Intensive Care. Echter niet elke kliniek beschikt over deze faciliteiten, en zal kunnen voldoen aan randvoorwaarden. Uiteraard heeft intubatie en invasieve mechanische ventilatie alleen een plaats op de IC.

Op basis van expert opinion adviseert zij om:

- Arteriële zuurstofsaturatie (PaO_2) en perifere saturatie (SpO_2) aan het begin van de behandeling aan elkaar te correleren;
- Minimaal te meten tijdens gebruik van HFNO en CPAP zijn SpO_2 en ademfrequentie.
 - Meet deze bij voorkeur continu, doch tenminste à 15 minuten gedurende de eerste 2 uur
 - Bij een stabiele patiënt kan deze frequentie daarna afgebouwd worden naar een meting elke 30 minuten.
 - Als de patiënt stabiel blijft na 6 uur monitoring kan dit verder worden afgebouwd tot 1 keer per uur.

Het is van belang tijdig te onderkennen dat een patiënt, eenmaal gestart met niet-invasieve ademhalingsondersteuning, respiratoir verslechtert, zodat deze, indien nodig naar de intensive care kan worden verplaatst om daar intensiever behandeld te worden of zo nodig geïntubeerd te worden. In de literatuur wordt een scherpe discussie gevoerd over het optimale moment van endotracheale intubatie bij patiënten met COVID-19 (Gattinoni, 2021; Tobin, 2020; Tobin et al., 2020) waarbij mogelijk de longschade als gevolg van een verhoogde ademdrive zou toenemen in het geval van een uitgestelde intubatie. Deze 'patiënt self-inflicted lung-injury (P-SILI)' is een argument om patiënten met COVID-19 juist vroegtijdig invasief mechanisch te beademen. Tegenstanders van vroege intubatie wijzen op gebrek aan bewijs voor het bestaan van P-SILI en mag het gebruik van niet-invasieve ademhalingsondersteuning niet in de weg staan gezien het aantal ernstige complicaties dat gepaard gaat met intubatie en mechanische ventilatie.

Wanneer HFNO of CPAP op de verpleegafdeling is gestart, adviseert de werkgroep om een intensivist te consulteren voor overleg over vervolgbeleid (overname IC-afdeling met/zonder invasieve beademing) indien ondanks gebruik van HFNO met een flow van 60L/min en een FiO_2 van $\geq 60\%$ of CPAP met PEEP $\geq 10\text{cmH}_2\text{O}$ en een FiO_2 van $\geq 60\%$ er sprake is van:

- $\text{PaO}_2 < 8\text{kPa}$ (60mmHg) of een perifere saturatie $< 92\%$; of
- tachypneu $> 30/\text{min}$; of gebruik van hulpademhalingspijpen

Zie voor de criteria ook het [stroomschema](#).

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep ziet voldoende argumenten om het gebruik van HFNO en/of CPAP bij hypoxemisch respiratoir falen ten gevolge van COVID-19 te overwegen, wanneer bovengenoemde randvoorwaarden aanwezig zijn. Ten opzichte van COT voorkomt niet-invasieve ademhalingsondersteuning mogelijk intubatie. Het beperkt aantal relevante studies dat beschikbaar is toont voornamelijk geen duidelijk voordeel of nadeel voor het gebruik van HFNO of CPAP. De definitievere peer-reviewed uitkomsten van de RECOVERY-RS studie en

soortgelijke studies die lopen, gaan hier wellicht een ander licht op laten schijnen. Eveneens zijn er voorlopig geen aanwijzingen dat een behandeling met niet-invasieve ademhalingsondersteuning ten opzichte van vroege intubatie leidt tot slechtere uitkomsten.

Onderbouwing

Achtergrond

Bij klinische patiënten met COVID-19 is vaak sprake van voornamelijk hypoxisch respiratoire falen. Een deel van deze patiënten zal uiteindelijk invasief beademd worden. Behalve invasieve beademing, kan men ook gebruik maken van niet-invasieve ademhalingsondersteuning, te weten nasale high flow therapie (HFNO) of CPAP. De vraag is of starten met HFNO of CPAP, vergeleken met COT/directe intubatie, een periode met invasieve beademing kan voorkómen.

HFNO kan bovendien gebruikt worden in een situatie waar besloten is dat een patiënt niet meer in aanmerking komt voor invasieve beademing. Het is de vraag of HFNO een meerwaarde heeft boven conventionele zuurstoftherapie bij deze categorie patiënten.

Conclusies / Summary of Findings

Conclusions *Subquestion-1a. Effectiveness of an initial trial of HFNO compared to early invasive mechanical ventilation*

No GRADE	<u>90-day mortality</u> No evidence was found regarding the effect of an initial trial of HFNO on 90-day mortality when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>mortality in ICU</u> No evidence was found regarding the effect of an initial trial of HFNO on mortality in ICU when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
Very low GRADE	<u>in-hospital mortality</u> The evidence is very uncertain about the effect of an initial trial of HFNO on in-hospital mortality when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: Mellado-Artigas et al., 2021</i>
Very low GRADE	<u>number of days in ICU</u> The evidence is very uncertain about the effect of an initial trial of HFNO on number of days in ICU when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: Mellado-Artigas et al., 2021</i>
No GRADE	<u>hospital length of stay</u> No evidence was found regarding the effect of an initial trial of HFNO on hospital length of stay when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>

Very low GRADE	<u>ventilator-free days</u> the evidence is very uncertain about the effect of an initial trial of HFNO on number of ventilation-free days when compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: Mellado-Artigas et al., 2021</i>

Subquestion-1b. Effectiveness of HFNO (in respiratory ward or ICU), compared to treatment with conventional oxygen therapy

No GRADE	<u>90-day mortality</u> No evidence was found regarding the effect of an initial trial of HFNO on 90-day mortality when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: Ospina-Tascón et al., 2021</i>
No Grade	<u>mortality in ICU</u> No evidence was found regarding the effect of an initial trial of HFNO on mortality in ICU when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>in-hospital mortality</u> No evidence was found regarding the effect of an initial trial of HFNO on in-hospital mortality when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
Very Low grade	<u>number of days in ICU</u> The evidence is very uncertain about the effect of an initial trial of HFNO results when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: Ospina-Tascón et al., 2021</i>
Very low GRADE	<u>hospital length of stay</u> The evidence is very uncertain about the effect of an initial trial of HFNO on hospital length of stay when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: Ospina-Tascón et al., 2021</i>
Low grade	<u>ventilator-free days</u> The evidence suggests that an initial trial of HFNO results in a reduction of ventilator-free days when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. - <i>Sources: Ospina-Tascón et al., 2021</i>

Low grade	<u>need for intubation</u> The evidence suggests that an initial trial of HFNO results in a reduction of need for intubation when compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. – <i>Sources: Ospina-Tascón et al., 2021</i>

Subquestion-2a: the effectiveness of an initial trial of CPAP, compared to early treatment with invasive mechanical ventilation

No GRADE	<u>90-day mortality</u> No evidence was found regarding the effect of an initial trial of CPAP on 90-day mortality compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>

No GRADE	<u>mortality in ICU.</u> No evidence was found regarding the effect of an initial trial of CPAP on mortality in ICU compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>in-hospital mortality</u> No evidence was found regarding the effect of an initial trial of CPAP on in-hospital mortality compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>number of days in ICU</u> No evidence was found regarding the effect of an initial trial of CPAP number of days in ICU compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>hospital length of stay</u> No evidence was found regarding the effect of an initial trial of CPAP hospital length of stay compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>hospital length of stay</u> No evidence was found regarding the effect of an initial trial of CPAP hospital length of stay compared to early invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>

- *Subquestion-2b: the effectiveness of CPAP (in respiratory ward or ICU), compared to treatment with conventional oxygen therapy*

No GRADE	<u>90-day mortality</u> No evidence was found regarding the effect of an initial trial of CPAP on 90-day mortality compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>
No GRADE	<u>in-hospital mortality</u> No evidence was found regarding the effect of an initial trial of CPAP on in-hospital mortality compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>

No GRADE	<u>hospital length of stay</u> No evidence was found regarding the effect of an initial trial of CPAP on hospital length of stay compared to conventional oxygen therapy in patients with acute respiratory failure due to COVID-19. <i>Sources: not applicable</i>

Samenvatting literatuur

Subquestion-1a. Effectiveness of an initial trial of HFNO, compared to early treatment with invasive mechanical ventilation (MV)

Mellado-Artigas et al. (2021) compared the use of HFNO as initial oxygenation strategy in the ICU to use of invasive mechanical ventilation in the first 24 hours of ICU admission. The decision to intubate was left to the treating physician. Patients having a respiratory rate >35/min, a GCS <13 or a pH <7.25 were excluded. The study included 122 (PCR confirmed) COVID-19 patients. Propensity score matching was used to adjust for measured confounding.

Subquestion-1b. Effectiveness of HFNO (in respiratory ward or ICU), compared to treatment with conventional oxygen therapy

Ospina-Tascón (2021) conducted a RCT in emergency departments and intensive care units in 3 hospitals in Colombia from August 2020 to February 2021. Adults with acute respiratory failure due to COVID-19 with a PaO₂/FiO₂ ratio < 200 were randomized to receive either HFNO at an initial flow of 60 L/min and an FiC₂ of 1.0. (n=99), or conventional oxygen therapy, applied continuously through any low-flow oxygen device (nasal prongs, mask with/without oxygen reservoir, Venturi mask) (n=100). In both groups, FiO₂ was adjusted to maintain SpO₂ ≥92% until patient intubation or recovery. Patients needing immediate endotracheal intubation or having a pCO₂ >55mmHg were excluded, as well as patients with severe CHF, advanced COPD or having do-not-intubate orders. Intervention and control group were comparable on age, respiratory rate, PaO₂/FiO₂ at randomization. Hazard ratios and proportional odds models adjusted for age, PaO₂/FiO₂ and comorbidities at randomization were calculated.

Results of studies

Subquestion-1a. Effectiveness of an initial trial of HFNO (in respiratory ward or ICU), compared to early treatment with invasive mechanical ventilation (MV)

90-day mortality (critical outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to MV on 90-day mortality.

Mortality in ICU (critical outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to MV on ICU-mortality.

In-hospital mortality (important outcome measure)

Only 1 study reported on in-hospital mortality when comparing HFNO to early treatment with invasive mechanical ventilation. In-hospital mortality in patients receiving HFNO was 15%, whereas mortality in patients receiving MV was 21% (OR 0.64 (95%CI 0.25 to 1.64)) (Mellado-Artigas, 2021). This means that patients receiving HFNO had a 36% lower risk on in-hospital mortality than patients receiving MV. This difference is clinically relevant.

Number of days in ICU (important outcome measure)

ICU length of stay was shorter for patients receiving HFNO (11 days) compared to patients receiving MV (20 days; mean difference -8.2 days (95%CI -12.7 to -3.6 days) (Mellado-Artigas, 2021). This is a clinically relevant difference.

Hospital length of stay (important outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to MV on hospital length of stay.

Ventilator-free days (important outcome measure)

Mellado-Artigas et al. (2021) reported a difference of 8.0 days (95% CI 4.4 to 11.7) in ventilator-free days in favor of the patient group receiving HFNO (21 days, N=61) over the patient group receiving MV (13 days, N=61). This is clinically relevant. The intubation rate in the HFNC group, after at least 1 day of HFNC, was 38%.

Subquestion-1b. Effectiveness of HFNO, compared to treatment with conventional oxygen therapy

90-day mortality (critical outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to conventional oxygen therapy on 90-day mortality. However, Ospina-Tascón, 2021) reported a difference on 28-day mortality instead: HR for death at day 28 was 0.49 (95% CI 0.21 to 1.16) in the HFNO group (N=8 (8.1%)) compared with the conventional oxygen therapy group (N=16 (16.0%)). This means that 28-day mortality in the conventional oxygen group is 50% lower for patients on HFNO compared to conventional oxygen. This difference is clinically relevant.

Mortality in ICU (critical outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to conventional oxygen therapy on mortality in ICU.

In-hospital mortality (important outcome measure)

The systematic literature search returned no comparative studies investigating the effect of HFNO compared to conventional oxygen therapy on in-hospital mortality.

Number of days in ICU (important outcome measure)

Ospina-Tascón (2021) reported a difference in number of days in ICU, these were 7 days (IQR 5 to 13) for patients receiving HFNO (N=99) and 9 days (IQR 9 to 23) for patients receiving conventional oxygen therapy (N=100). OR was 0.74 (95% CI 0.45 to 1.22). This means that number of days in ICU was 26% lower for patients receiving HFNO than for patients receiving conventional oxygen therapy. This difference is clinically relevant.

Hospital length of stay (important outcome measure) Ospina-Tascón (2021) did find a difference in hospital length of stay: hospital length of stay, as this was 12 days (IQR 9-20) in the HFNO group (N=99), and 14 days (IQR 9-23) in the conventional oxygen group (N=100), OR is 0.77 (95% CI 0.47 to 1.25). This is a clinically relevant difference.

Ventilator-free days (important outcome measure)

In the study by Ospina-Tascón (2021), median ventilator-free days within the first 28 days after randomization was lower for the HFNO than the conventional oxygen group. These were 28 (IQR 19-28) days in the HFNO group (N=99) vs 24 (IQR 14-28) days in the conventional oxygen therapy group (N=100), respectively (OR 2.08 (95% CI 1.18 to 3.64)). Patients on HFNO thus had more ventilator-free days than patients on conventional oxygen therapy. This difference is clinically relevant.

Need for intubation (important outcome measure)

In the study by Ospina-Tascón (2021), 34 (34.3%) of HFNO patients and 51 (51.0%) of patients on conventional oxygen therapy had been intubated by day 28 after randomization. HR was 0.62 (95% CI 0.39 to 0.96), in favor of HFNO. This means that patients on HFNO have a 38% lower chance on intubation than patient on conventional oxygen. This is clinically relevant and statistically significant.

Level of evidence of the literature

Subquestion-1a. Effectiveness of an initial trial of HFNO (in respiratory ward or ICU), compared to early treatment with invasive mechanical ventilation (MV)

The domain of the literature search question is intervention. Therefore, observational studies start at low GRADE.

In-hospital mortality: the level of evidence was downgraded by 1 level, due to limitations in study design (risk of bias, -1) and by 2 levels due to imprecision.

Number of days in ICU: the level of evidence was downgraded by 1 level, due to limitations in study design (risk of bias, -1)

Ventilator-free days: the level of evidence was downgraded by 1 level, due to limitations in study design (risk of bias, -1) and by 2 levels due to imprecision (-1)

90-day mortality, mortality in ICU and hospital length of stay: the level of evidence was not graded due to no available data.

Subquestion-1b. Effectiveness of HFNO, compared to treatment with conventional oxygen therapy
RCT's start at high GRADE

90-day mortality: the level of evidence was downgraded by 3 levels because of no possibility of blinding (risk of bias, -1), indirectness (28-day mortality instead of 90-day mortality) and the confidence interval crosses the boundaries of clinical relevance (imprecision, -2).

Number of days in ICU: the level of evidence was downgraded by 2 levels, because of no possibility of blinding (risk of bias, -1), and the confidence interval crosses the boundaries of clinical relevance (imprecision, -2).

Hospital length of stay: the level of evidence was downgraded by 2 levels, because of no possibility of blinding (risk of bias, -1), and the confidence interval crosses the boundaries of clinical relevance (imprecision, -2).

Ventilator-free days: the level of evidence was downgraded by 2 levels, because of no possibility of blinding (risk of bias, -1), and the confidence interval crosses the boundaries of clinical relevance (imprecision, -1).

Need for intubation: the level of evidence was downgraded by 2 levels, because of no possibility of blinding (risk of bias, -1), and the confidence interval crosses the boundaries of clinical relevance (imprecision, -1).

Mortality in ICU and in-hospital mortality: the level of evidence was not graded due to no available data.

Summary of literature continuous positive airway pressure (CPAP)

Results

Summary of literature

For subquestion-2a and subquestion-2b the literature search returned no studies investigating the crucial and important outcome measures.

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Results of studies

Subquestion-2a: the effectiveness of an initial trial of CPAP, compared to early treatment with invasive mechanical ventilation

The literature search returned no studies investigating the crucial and important outcome measures.

Subquestion-2b: the effectiveness of CPAP, compared to treatment with conventional oxygen therapy

The literature search returned no studies investigating the crucial and important outcome measures.

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Level of evidence of the literature

Subquestion-2a. Effectiveness of an initial trial of CPAP (in respiratory ward or ICU), compared to early treatment with invasive mechanical ventilation

Due to the absence of comparative studies, the level of evidence for all outcome measures could not be assessed.

Subquestion-2b. Effectiveness of CPAP compared to treatment with conventional oxygen therapy

Due to the absence of comparative studies, the level of evidence for all outcome measures could not be assessed.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

Subquestion-1a. What is the effectiveness of an initial trial of HFNO (in respiratory ward or ICU), compared to early treatment with invasive mechanical ventilation (MV) in patients with acute respiratory failure due to COVID-19?

- P: adults with COVID-19 infection and acute respiratory failure needing ventilatory support
- I: high flow nasal cannula (HFNO), high flow oxygen therapy
- C: invasive mechanical ventilation
- O: 90-day mortality, mortality in ICU, in-hospital mortality, number of days in ICU, hospital length of stay, ventilator-free days

Subquestion-1b. What is the effectiveness of HFNO, compared to treatment with conventional oxygen therapy in patients with acute respiratory failure due to COVID-19?

- P: adults with COVID-19 infection and acute respiratory failure needing ventilatory support
- I: high flow nasal cannula (HFNO), high flow oxygen therapy
- C: conventional oxygen therapy
- O: 90-day mortality, mortality in ICU, in-hospital mortality, number of days in ICU, hospital length of stay, need for intubation, ventilator-free days

Subquestion-2a. What is the effectiveness of an initial trial of CPAP, compared to early treatment with invasive mechanical ventilation in patients with acute respiratory failure due to COVID-19

- P: adults with COVID-19 infection and acute respiratory failure needing ventilatory support
- I: continuous positive airway pressure (CPAP)
- C: invasive mechanical ventilation
- O: 90-day mortality, mortality in ICU, in-hospital mortality, number of days in ICU, hospital length of stay, ventilator-free days

Subquestion-2b. What is the effectiveness of CPAP compared to treatment with conventional oxygen therapy in patients with acute respiratory failure due to COVID-19?

- P: adults with COVID-19 infection and acute respiratory failure needing ventilatory support
- I: continuous positive airway pressure (CPAP)
- C: conventional oxygen therapy
- O: 90-day mortality, in-hospital mortality, hospital length of stay

Relevant outcome measures

For all subquestions, 90-day mortality and number of days in ICU were considered critical outcome measures for decision making; ICU mortality, in-hospital-mortality, hospital length of stay and ventilator-free days were considered important outcome measures for decision making. For subquestions 1a and 1b, need for intubation was also considered an important outcome measure.

The working group did not define the outcome measures listed above a priori, but used the definitions used in the studies.

The working group defined the following differences as a minimal clinically (patient) important difference

- Mortality: $\geq 10\%$
- Number of days in ICU: ≥ 1 day
- Length of hospital stay: ≥ 1 day
- Need for intubation: $\geq 10\%$
- Ventilator-free days: ≥ 1 day

Search and select (Methods)

For the first edition of this report, one search strategy was performed for 3 subquestions (HFNCO, CPAP, BiPAP). The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 1-7-2020. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 407 hits. Studies were selected based on the following criteria: RCT's, cohort studies or case-control studies comparing HFNO, CPAP or NIV with invasive mechanical ventilation or conventional oxygen therapy in patients with COVID-19, SARS or MERS. Eleven studies were initially selected based on title and abstract screening. After reading the full text, 9 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 2 studies were included (Alraddadi, 2019; Yam, 2005). For the second edition of this report, the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 1-3-2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 3126 hits. Studies were selected based on the following criteria: RCT's, cohort studies or case-control studies comparing HFNO, CPAP or NIV with invasive mechanical ventilation or conventional oxygen therapy. From 1-7-20 onward, only studies in patients with COVID-19, not SARS or MERS, were included. This resulted initially in 48 selected studies, based on title and abstract screening. After reading the full text, 46 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 2 studies were included (Mellado-Artigas, 2021; Teng, 2020). For this third edition, the databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 20-12-2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 2933 hits. Studies were selected based on the following criteria: RCT's, cohort studies or case-control studies comparing HFNO, CPAP or NIV with invasive mechanical ventilation or conventional oxygen therapy. This resulted initially in 30 selected studies, based on title and abstract screening. As it was then decided by the working group to include only HFNO and CPAP in the update of this guideline, only studies concerning HFNO (25 studies) and CPAP (2 studies) were read full text. After reading

the full text, 24 studies on HFNCO were excluded (see the table with reasons for exclusion under the tab Methods), and 1 additional study was included (Ospina-Tascón, 2021). After reading the full text, both studies on CPAP were excluded, no additional studies were included.

Summary of literature high flow nasal therapy (HFNO)

Results

For subquestion-1a one cohort study was described in version 2.0 of this guideline comparing the effect of HFNO to early initiation of mechanical ventilation (Mellado-Artigas et al., 2021). No additional studies were found. For subquestion-1b one randomized trial (Teng et al., 2020) (described in version 2.0) was replaced by the RCT by (Ospina-Tascón, 2021) as this RCT was of better quality and described more outcome variables. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 29-09-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Niet-invasieve ademhalingsondersteuning – organisatie van zorg

Uitgangsvraag

Welke criteria bepalen of een patiënt voor HFNO of CPAP kan worden opgenomen op de verpleegafdeling of op de IC?

Aanbeveling

Stem voorwaarden voor HFNO en/of CPAP bij patiënten met COVID-19 en de afdeling waar dit kan worden gegeven af met betrokken specialisten. Leg deze afspraken vast in een lokaal protocol.

Start HFNO en/ of CPAP bij COVID-19-patiënten alleen als:

- er voldoende ervaren en geschoold personeel beschikbaar is, én
- er voldaan kan worden aan de voorwaarden van monitoring, én
- de patiënt kan worden opgenomen in (cohort)-isolatie en er voldoende beschermingsmaterialen voor het personeel beschikbaar zijn

De volgende criteria zijn redenen voor direct overleg met intensivist (mits wel-beademen beleid) bij patiënten met hypoxemisch respiratoir falen en COVID-19:

- $\text{pH} < 7,35$ op basis van een respiratoire acidose
- Levensbedreigende hypoxemie ($\text{PaO}_2 < 8 \text{ kPa}$ of 60 mmHg ondanks 15 L/min via NRM)
- Stoppen met ademen (contact reanimatieteam i.p.v. intensivist)
- Overmatige sputumproductie
- Bij (verhoogd risico op) aspiratie
- Afwezigheid van hoest- en/of slikreflexen
- Psychomotore onrust
- Verminderd bewustzijn ($\text{EMV} < 10$)
- Hemodynamische instabiliteit waarvoor vasopressie nodig

Bij patiënten met COVID-19 en een behandeling gericht op comfort en niet op genezing heeft (niet-)invasieve ademhalingsondersteuning geen plaats.

Overwegingen

Niet-invasieve ademhalingsondersteuning bij patiënten met COVID-19 wordt op dit moment zowel op de intensive care als op de verpleegafdeling opgestart. Niet het type afdeling, maar het kunnen voldoen aan de in deze richtlijn beschreven randvoorwaarden moet leidend zijn in het oordeel waar niet-invasieve ademhalingsondersteuning te starten. Deze voorwaarden dienen binnen de organisatie te worden afgestemd. Deze voorwaarden en zo nodig andere afspraken moeten worden vastgelegd in een lokaal protocol. Voor organisatie van zorg is geen literatuuronderzoek verricht. Overwegingen en aanbevelingen berusten op extrapolatie van andere richtlijnen, expert opinion en consensus binnen de werkgroep.

Organisatorisch

Voor alle vormen van ademhalingsondersteuning is het een voorwaarde, dat voldoende geschoold en voldoende ervaren personeel beschikbaar moet zijn. Voor alle voorbehouden handelingen moet worden aangegeven of men bekwaam is. De eisen aan de afdeling om dit succesvol te implementeren zijn conform de richtlijnmodule 'eisen afdeling voor NIV bij COPD'. Verder is het een voorwaarde dat behandeling plaatsvindt in een geschikte ruimte met apparatuur die recht doet aan het convenant 'veilige toepassing van medische technologie'. Omdat er gewerkt wordt met hoge fractie zuurstof is met name brandveiligheid van belang. Met name HFNO maakt gebruik van hoge flow; zuurstofleidingen kunnen deze in beperkte mate leveren. Het aantal aan te sluiten HFNO-apparaten op een leiding is daarmee beperkt. Daarmee moet, gezien de apparaten gemakkelijk bedside zijn aan te sluiten, tevoren rekening worden gehouden. Tenslotte is het een voorwaarde dat een patiënt met COVID-19 en noodzaak tot niet-invasieve ademhalingsondersteuning alleen op een verpleegafdeling kan worden opgenomen als er mogelijkheden zijn voor (cohort-)isolatie en als er voldoende beschermingsmaterialen zijn voor personeel. Zie daarvoor ook de leidraad Persoonlijke bescherming in de (poli)klinische setting vanwege SARS-CoV-2. Er is discussie over het omgaan met de risico's van niet-invasieve ademhalingsondersteuning bij COVID-19-patiënten vanwege aerosolvorming. Voor adviezen over bescherming bij aerosolvormende procedures wordt verwezen naar de Leidraad Medische procedures die een infectieuze aerosol genereren (IAGP) met SARS-CoV-2 (vervallen). Deze leidraad wordt, op basis van literatuuronderzoek, periodiek geüpdatet. Het is daarom raadzaam, bij twijfel over het risico van aerosolvorming bij non-invasieve ademhalingsondersteuning deze leidraad te raadplegen.

Medisch-inhoudelijk

Niet elke COVID-19 patiënt met hypoxemisch respiratoir falen zal geschikt zijn voor een behandeling met een vorm van niet-invasieve ademhalingsondersteuning op de afdeling. Bovendien kan sprake zijn van co-morbiditeit of falen van meerdere orgaansystemen waardoor starten van niet-invasieve ademhalingsondersteuning niet de voorkeur heeft. De werkgroep adviseert om **direct invasieve beademing** te overwegen bij patiënten met een "wel-beademen-beleid" en:

- pH < 7,35 op basis van een respiratoire acidose
- Levensbedreigende hypoxemie (PaO₂ <8kPa of 60 mmHg ondanks 15 L/min via NRM)
- Stoppen met ademen (contact reanimatieteam i.p.v. intensivist)
- Overmatige sputumproductie
- Bij (verhoogd risico op) aspiratie
- Afwezigheid van hoest- en/of slikreflexen
- Psychomotore onrust
- Verminderd bewustzijn (EMV <10)
- Hemodynamische instabiliteit waarvoor vasopressie nodig is

Ten aanzien van de monitoring van patiënten aan de niet-invasieve ademhalings-ondersteuning verwijst de werkgroep naar de module over HFNO en CPAP en het bijbehorende stroomschema. Ook bij patiënten met een 'niet invasief beademen beleid', kan niet-invasieve ademhalingsondersteuning op de afdeling gestart worden, wanneer gedacht wordt dat de behandeling leidt tot herstel van de patiënt.

De werkgroep is van mening dat patiënten met een palliatief beleid en de diagnose COVID-19 niet in aanmerking komen voor zowel invasieve als niet-invasieve ademhalings-ondersteuning. Met een palliatief beleid wordt bedoeld een behandeling enkel gericht op comfort, zonder kans op genezing. Op welke manier deze patiëntengroep het best begeleid kan worden valt buiten het bestek van deze richtlijn.

Onderbouwing

Verantwoording

Laatst beoordeeld : 29-09-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Invasieve beademing bij COVID-19

Waar gaat deze richtlijnmodule over?

Deze richtlijnmodule behandelt de principes voor invasieve beademing bij patiënten met COVID-19-gerelateerd hypoxemisch falen. De plaats van vroege endotracheale intubatie wordt behandeld, evenals de optimale positieve eind-expiratoire druk (PEEP). De indicaties en randvoorwaarden voor niet-invasieve ademhalingsondersteuning bij patiënten met COVID-19 worden in andere modules behandeld.

Voor wie is deze richtlijnmodule bedoeld?

Deze richtlijnmodule is bedoeld voor alle zorgprofessionals die betrokken zijn bij invasieve beademing van patiënten met COVID-19-gerelateerd hypoxemisch falen.

Voor patiënten

In het ziekenhuis kunt u meer behandelingen krijgen dan thuis of in een verpleeghuis. Bijvoorbeeld meer medicijnen en meer zuurstof. Als u meer zorg nodig heeft, kunt u opgenomen worden op de intensive care (IC). Daar moet u soms beademd worden. Of dit in uw situatie kan en zin heeft, beslist de specialist in het ziekenhuis samen met u.

Zie ook de informatie op Thuisarts.nl:

<https://www.thuisarts.nl/corona-in-ziekenhuis/ik-heb-corona-en-krijg-behandeling-in-ziekenhuis>

Hoe is de richtlijnmodule tot stand gekomen?

Op initiatief van de Federatie Medisch Specialisten is begin 2021 gestart met de ontwikkeling van de richtlijn COVID-19. Deze richtlijn beschrijft de infectiepreventie, diagnostiek, behandeling en revalidatie en nazorg voor alle COVID-19 (verdachte) patiënten. Hierbij is op initiatief van diverse wetenschappelijke verenigingen een aantal aanvullende modules ontwikkeld, waaronder over invasieve beademing. Voor de module over invasieve beademing bij COVID-19 is begin 2022 een multidisciplinaire werkgroep ingesteld, bestaande uit vertegenwoordigers van alle relevante specialismen. Daarnaast is er aandacht besteed aan het patiëntenperspectief door het meelesen van de patiëntenorganisatie Stichting Family and patient Centered Intensive Care (FCIC) en IC Connect. De verkregen input is meegenomen bij het opstellen van de modules.

Status van de richtlijn

Gedurende de pandemie zijn diverse leidraden gepubliceerd. Voor onderwerpen die momenteel (nog) niet als modules zijn gepubliceerd, verwijzen we u naar de website:

<https://www.demedischspecialist.nl/onderwerp/details/richtlijnen-handreikingen-leidraden>.

Verantwoording

Laatst beoordeeld : 09-02-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Timing

Uitgangsvraag

Wat is de plaats van vroege endotracheale intubatie van patiënten met COVID-19 gerelateerd hypoxemisch falen?

Aanbeveling

Bepaal het moment van endotracheale intubatie op basis van de ernst van symptomen en klachten (respiratoire insufficiëntie, risico aspiratie). Er is geen plaats voor endotracheale intubatie om pulmonale schade ten gevolge van hoge adem effort (P-SILI) te voorkomen.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er werd geen vergelijkende literatuur gevonden die richting kon geven aan klinische besluitvorming voor vroege versus latere start van invasieve beademing bij patiënten met COVID-19. Hier ligt een kennislacune. De aanbeveling zal daarom gebaseerd worden op andere overwegingen waaronder expert opinie, waar mogelijk onderbouwd met (indirecte) literatuur.

Bij IC-patiënten is langere duur van invasieve beademing is geassocieerd met mortaliteit, morbiditeit, belasting van ziekenhuiszorg en langdurige klachten na ontslag uit ziekenhuis. Vanuit dit principe zou gebruik van noninvasieve respiratoire ondersteuning zo lang mogelijk toegepast moeten worden om endotracheale intubatie te voorkomen. Een strategie van vroege intubatie kan leiden tot intubatie van patiënten die ook behandeld hadden kunnen worden met non-invasieve ademhalingsondersteuning (high flow nasal oxygen, HFNO of noninvasieve ventilatie, NIV; zie daarvoor de module niet-invasieve beademing bij COVID-19). Een potentieel nadeel van latere endotracheale intubatie is dat patiënten met hoge ademarbeid, grote pleurale drukwisselingen kunnen genereren wat zou kunnen leiden tot longschade, de zogenaamde "*patient self-inflicted lung-injury*" (P-SILI) (Brochard, 2017). Bij patiënten met acuut hypoxemisch falen (non-COVID-19) ondersteund met NIV, is hogere ademinspanning (delta Pes) geassocieerd met NIV falen, wat volgens de auteurs een argument is voor het bestaan van P-SILI (Tonelli, 2020). Esnault (2020) vond dat bij patiënten met COVID-19 die endotracheaal geïntubeerd waren en in ontwenfase waren, hoge ademinspanning het risico op respiratoire achteruitgang (gaswisseling) verhoogt, passend bij P-SILI. Dit manuscript was wel aanleiding tot forse discussie (Tobin, 2020; Tobin, 2021; Gattinoni, 2021), die zowel de techniek om effort te meten betrof, alsook het bewijs voor bestaan van P-SILI. Overigens lijkt de respiratoire drive en effort bij patiënten met ernstig hypoxemisch falen ten gevolge van COVID-19 die nog niet geïntubeerd zijn zelfs lager dan van patiënten met niet-COVID-19 gerelateerde hypoxemie (Tonelli, 2020). Zoals hierboven genoemd zijn er geen gerandomiseerde studies naar vroege versus latere intubatie bij patiënten met COVID-19. Interessant is een multicenter observationele studie waarin patiënten met vroege intubatie (<24 uur ICU opname) werden vergeleken met patiënten die initieel behandeld werden met HFNO. Na propensity matching (N=61 per groep), was het aantal *ventilator-free days* op dag 28 hoger en de IC-opnameduur korter in de HFNO groep. Er was geen verschil in mortaliteit. In de HFNO groep werd uiteindelijk 38% van de patiënten geïntubeerd. Vergelijken van patiënten die vroeg versus later geïntubeerd werden, toonde geen verschil in ventilator-free days, IC-opnameduur of mortaliteit (Mellado-Artigas, 2021). Dus op basis van de kennis van de fysiologie en deze observationele studie is onvoldoende reden om aan te

nemen dat patiënten met hypoxemisch falen ten gevolge van COVID-19 meer risico lopen op P-SILI als endotracheale intubatie wordt uitgesteld tot niet invasieve ondersteuning faalt. Wel lijkt vroege intubatie te leiden tot meer intubaties en langere IC-opnameduur.

De werkgroep ziet onvoldoende aanwijzingen voor “vroege endotracheale intubatie” om risico van P-SILI te verminderen of patiëntrelevante uitkomsten te verbeteren bij patiënten met COVID-19. Met andere woorden, criteria voor endotracheale intubatie zijn gelijk aan die voor andere oorzaken voor hypoxemisch falen, en richten zich vooral op ernst van symptomen en minder op de duur daarvan.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Endotracheale intubatie met diepe sedatie heeft grote gevolgen voor de patiënt. De patiënt verliest de mogelijkheid tot communicatie en dus ook de mogelijkheid om behandelwensen kenbaar te maken aan familie en professionals. Het proces van ontwennen van invasieve beademing is voor veel patiënten zeer belastend en soms zelfs traumatisch. Dit zijn vanuit patiënt perspectief belangrijke argumenten om endotracheale intubatie zo lang mogelijk uit te stellen. Daar tegenover staat dat voor patiënten met dyspneusensatie, of ongerief gerelateerd aan COVID-19 juist als positief kan worden ervaren (“rust krijgen; onvermijdelijk”).

Kosten (middelenbeslag)

Invasieve mechanische ventilatie is een medische behandeling voor patiënten met ernstig COVID-19 gerelateerde hypoxemie. Deze behandeling wordt alleen toegepast op een intensive-careafdeling. De kosten hiervoor zijn hoog. Vanuit sociaal-economisch perspectief heeft behandeling met niet-invasieve respiratoire ondersteuning voor patiënten met COVID-19 en hypoxemisch falen de voorkeur. Vroege endotracheale intubatie, waarbij risico bestaat dat patiënten invasief beademd worden die dit uiteindelijk niet nodig blijken te hebben, leidt tot onnodige belasting van financiële middelen en andere resources.

Aanvaardbaarheid, haalbaarheid en implementatie

Voor invasieve mechanische ventilatie, alleen toegepast op de intensive-careafdeling, is een team van gespecialiseerde verpleegkundigen en artsen nodig. De capaciteit van IC-bedden in Nederland is beperkt. Vroeg inzetten van invasieve mechanische ventilatie heeft daarom niet de voorkeur (zie ook onder kosten).

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep ziet onvoldoende aanwijzingen voor vroege endotracheale intubatie om risico van P-SILI te verminderen of patiënt uitkomsten te verbeteren bij patiënten met COVID-19 met acuut hypoxemisch falen. Vroege endotracheale intubatie, waarbij risico bestaat dat patiënten invasief beademd worden die dit uiteindelijk niet nodig blijken te hebben, leidt tot onnodige belasting van financiële middelen en andere resources.

Onderbouwing

Achtergrond

Noninvasieve respiratoire ondersteuning door middel van *high flow nasal oxygen* (HFNO) of noninvasieve ventilatie (NIV) wordt frequent toegepast bij COVID-19 patiënten met acuut hypoxemisch falen om het risico op endotracheale intubatie en de daarmee geassocieerde risico's te verlagen. In de literatuur wordt een

scherpe discussie gevoerd over het optimale moment van endotracheale intubatie bij patiënten met COVID-19 (Tobin, 2020; Tobin, 2021; Gattinoni, 2021). De essentie van deze discussie is dat "latere intubatie" in vergelijking met "vroeg intubatie" longschade kan verergeren door mogelijk hoge respiratoire drive bij patiënten met COVID-19 en zo het risico op zogenaamde "*patiënt self-inflicted lung-injury*" (P-SILI). Het ontwikkelen van P-SILI zou dus een argument zijn voor intubatie in de vroege fase van hypoxemisch falen. Tegenstanders van vroeg intubatie wijzen op gebrek aan bewijs voor het bestaan van P-SILI en de nadelen van misschien zelfs onnodige intubatie en invasieve beademing, zoals diafragmazwakte en hogere kosten. Het is hierbij belangrijk op te merken dat er geen objectieve definities zijn wat vroege en wat latere intubatie is, dit verschilt per land en per onderzoek. Het patiëntperspectief is hierbij relevant, zeker bij COVID-19, omdat deze patiënten vaak minder dyspneu ervaren bij hypoxemie. Helaas zijn geen studies gepubliceerd die dyspneu sensatie, of comfort niveau onderzocht hebben. Daarom wordt dit niet meegenomen in deze richtlijn.

Conclusies / Summary of Findings

- GRADE	It was not possible to draw conclusions or grade the level of evidence for any outcome, due to the absence of randomized clinical trials comparing early and late start of mechanical ventilation.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the (un)favorable effects of early start compared to later start of invasive mechanical ventilation in patients with COVID-19?

P: patients with COVID-19 associated hypoxemic failure;

I: early start of invasive mechanical ventilation;

C: later start of invasive mechanical breathing;

O: mortality in ICU, in-hospital mortality, ICU length of stay, hospital length of stay, ventilator-free days.

Relevant outcomes

The guideline development group considered outcome mortality as a critical outcome measure for decision making; and outcomes ICU length of stay, hospital length of stay and ventilator-free days as important outcome measures for decision making.

The working group did not define early and late start of mechanical ventilation a priori, but followed the definitions used in literature. For the outcomes, the working group followed the definitions used in the studies.

As minimal clinically (patient) important differences, the working group used 3% for mortality (risk ratio, RR), 1 day for ICU length of stay and ventilator-free days, 3 days for hospital length of stay, 10% for continuous outcomes and 0.5 for standardized mean differences.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms

until January 28, 2022. The detailed search strategy is depicted under the Methods tab. The systematic literature search resulted in 235 hits. Studies were selected based on the following criteria: randomized clinical trials comparing early and late (or no) start of invasive mechanical ventilation in COVID-19 patients. Based on title and abstract screening, 15 studies were initially selected. After reading the full text, all studies were excluded (see the table with reasons for exclusion under the Methods tab).

Results

No prospective intervention studies conform the PICO were identified.

Verantwoording

Laatst beoordeeld : 09-02-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

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PEEP

Uitgangsvraag

Wat is het optimale positieve eind-expiratoire druk (PEEP) niveau voor patiënten met COVID-19 gerelateerd hypoxemisch falen die gecontroleerd beademd worden?

Aanbeveling

Titreer PEEP bij patiënten met COVID-19 gerelateerd hypoxemisch falen op basis van individuele patiëntkarakteristieken en niet op basis van een standaard hogere of lagere instelling.

Stel bij patiënten met COVID-19 gerelateerd hypoxemisch falen de optimale PEEP in met een breed beschikbare methode op basis van de lokale beschikbaarheid en eenvoudigheid van de meting, zoals

- PEEP/FiO₂-tabel;
- PEEP-titratie op basis van optimale respiratoire compliantie.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek verricht naar de gunstige en ongunstige effecten van hogere versus lagere PEEP bij invasieve beademing van patiënten met COVID-19 gerelateerd hypoxemisch falen. Er werden geen gerandomiseerde studies gevonden die richting kunnen geven aan de klinische besluitvorming. Hier ligt een kennislacune. De aanbeveling is daarom gebaseerd op andere argumenten waaronder expert opinie en indirecte literatuur, waarbij met name observationele studies richting geven.

Allereerst geldt de vraag, is de ademmechanica daadwerkelijk verschillend tussen COVID-19 gerelateerd hypoxemisch falen en non-COVID ARDS? Studies wijzen over het algemeen op een vergelijkbare compliantie tussen beide syndromen (Chiumello, 2020; Grieco, 2020; Grasselli, 2021; Fusina, 2022, Vandenbunder, 2021). In kleine populaties werd aanvankelijk onderscheid gemaakt tussen het zogenaamde L-type en het H-type van COVID-19 gerelateerd hypoxemisch falen, maar in grotere observationele studies blijkt dat de compliantie één continuüm is, vergelijkbaar met non-COVID ARDS. (Gattinoni, 2020; Grasselli, 2021; Vandenbunder, 2021). Daarom wordt het onderscheid in L-type en H-type in deze richtlijn niet gemaakt.

De effecten van PEEP zijn variabel, blijkend uit verschillende observationele studies. Zo zijn er studies die wijzen op een gebrek aan recruteerbaarheid bij hogere PEEP (Ball, 2021; Sang, 2021; Mauri, 2021), studies die wijzen op een toegenomen hyperinflatie met hogere PEEP (Mauri, 2021; Protti, 2022), studies die wijzen op een betere balans tussen hyperdistentie en collaps bij een hogere PEEP (Perier, 2020) en studies die wijzen op een betere oxygenatie bij een hogere PEEP (Grieco, 2020; Mittermaier, 2020; Protti, 2022). Naast de variabele effecten van PEEP op de respiratoire mechanica en oxygenatie, zijn er ook effecten op de circulatie en organen anders dan de long. Zo werd meer acuut nierfalen geobserveerd in patiënten met een hogere PEEP (Valk, 2021; Ottolina, 2022). De variabiliteit van de effecten van PEEP tussen en binnen deze studies kan veroorzaakt zijn door kleine aantallen patiënten, verschillende patiëntkarakteristieken, verschillende beademingsinstellingen, verschillende effectmetingen en verschillende meetmomenten. Hierdoor kunnen we enkel concluderen dat de respiratoire mechanica in COVID-19 gerelateerd hypoxemisch falen dusdanig heterogeen is, dat de vergelijking tussen hoge PEEP en lage PEEP in het algemeen geen praktische vergelijking is (Chiumello, 2021; Mauri, 2021).

Een manier om hiermee om te gaan is te zoeken naar geïndividualiseerde PEEP, waarbij de vraag is hoe het optimale PEEP niveau kan worden gevonden voor de individuele patiënt. Er zijn verschillende methodes onderzocht, zoals kwantitatieve CT-metingen, transpulmonale druk (TPP) metingen met behulp van oesofagus ballon, Peep/FiO₂-tabel, PEEP-titratie op basis van oxygenatie of compliantie, longechografie, Electrical Impedance Tomography (EIT)-metingen en een R/I (Recruitment/Inflation) ratio. Drie kleine studies vergeleken een EIT-gebaseerde PEEP-titratie met een PEEP/FiO₂-tabel en vonden een grote variabiliteit tussen de optimale PEEP per methode (Sella, 2020; Van der Zee, 2020; Gibot, 2021). Voor het gebruik van een PEEP/FiO₂-tabel wordt gewaarschuwd dat een hoge PEEP/FiO₂-tabel van de EpVent-2-studie (Beitler, 2019) kan leiden tot hyperinflatie (Chiumello, 2021). De overdistentie bij hogere PEEP bleek ook uit een studie waarbij hogere PEEP (16 cmH₂O) met lagere PEEP (8 cmH₂O) werd vergeleken middels luchthoudendheid op CT-scans (Ball, 2021). Er zijn onvoldoende studies naar welke methode van PEEP-titratie het beste is. Daarom is geen advies te geven welke methode het beste is. In de dagelijkse praktijk zal ook de beschikbaarheid van diagnostische middelen een belangrijke rol spelen. Methodes waar geen geavanceerde technieken voor nodig zijn, zijn een decremental PEEP-titratie op statische compliantie, een quasi-statische druk/volume curve (P/V-tool) en een PEEP/FiO₂-tabel. Indien geavanceerdere technieken beschikbaar zijn, kunnen deze gebruikt worden om richting geven aan een optimaal PEEP niveau, in het bijzonder bij complexe patiënten, zonder dat deze methodes duidelijk beter zijn dan de minder geavanceerde technieken. Gezien bestaande literatuur lijkt transpulmonale druk meting met oesofagusballon voorsnag de voorkeur te hebben boven andere geavanceerde monitoring technieken (Talmor, 2008; Beitler, 2019; Sarge, 2021).

De werkgroep ziet voorsnag onvoldoende bewijs voor een hogere of lagere PEEP bij COVID-19 gerelateerd hypoxemisch falen, maar adviseert een individuele PEEP-titratie. Geadviseerd wordt PEEP te titreren op basis van de respiratoire mechanica, gaswisseling en hemodynamiek. Qua respiratoire mechanica kan de PEEP worden getitreerd op de optimale respiratoire compliantie, middels een decremental PEEP-titratie of P/V-tool, omdat deze methodes laagdrempelig inzetbaar zijn. Indien dit onbevredigend is, kan een TPP- (of eventueel EIT) verder richting geven. De PEEP kan vervolgens verder worden aangepast op basis van gaswisseling en hemodynamiek. Zie ook de ARDS richtlijn (in ontwikkeling).

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Er is geen informatie bekend over patiëntvoorkeuren met betrekking tot hoge en lage PEEP. Het is niet waarschijnlijk dat het niveau van PEEP invloed heeft op de beleving van de patiënt, aangezien dit met name plaatsvindt bij gesedeerde patiënten.

Kosten (middelenbeslag)

Het PEEP-niveau zelf leidt niet tot extra kosten. Voor het vinden van de optimale individuele PEEP zijn hulpmiddelen beschikbaar die wel kunnen leiden tot extra kosten, zoals de EIT, TPP-metingen en CT-scans. Anderszins zou een optimale PEEP-instelling kunnen leiden tot een kortere beademings- en ligduur, wat vervolgens leidt tot verminderde kosten. Tot op heden is onvoldoende aangetoond dat het gebruik van geavanceerde pulmonale monitoring ook leidt tot een kortere beademings- en ligduur.

Aanvaardbaarheid, haalbaarheid en implementatie

Omdat er verschillende methodes zijn om PEEP in te stellen, is de haalbaarheid van de PEEP instelling geen probleem. Afhankelijk van wat er lokaal beschikbaar is, kan men een keuze maken voor de methode van voorkeur. Een dergelijke methode zal dan reeds geïmplementeerd zijn op de desbetreffende IC.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

De werkgroep adviseert tegen het standaard gebruik van een hogere of lagere PEEP-instelling bij patiënten met COVID-19 gerelateerd hypoxemisch falen. De gevonden literatuur kon geen richting geven aan de besluitvorming. Individualisering van PEEP-instelling is een logische manier om recht te doen aan de heterogene respiratoire mechanica. Met welke methode dit dient te gebeuren is niet duidelijk, maar men dient te beseffen dat bij een hogere PEEP het risico op hyperinflatie en orgaanfalen bestaat. Er bestaan geavanceerde methodes, zoals TPP-metingen, en eventueel EIT, maar ook methodes die breed beschikbaar zijn, zoals het gebruik van een PEEP/FiO₂-tabel, P/V-tool of een decremental PEEP-titratie op statische compliantie en/of gaswisseling. Laatstgenoemden hebben het voordeel dat er geen extra kosten aan verbonden zijn.

De werkgroep adviseert om eerst de PEEP te titreren voor een optimale respiratoire compliantie, waarbij de PEEP verder kan worden aangepast op basis van gaswisseling en hemodynamiek. Deze voorkeur berust op beschikbaarheid en eenvoudigheid van de meting.

Zie voor het instellen van PEEP bij non-COVID ARDS de richtlijn ARDS (in ontwikkeling).

Onderbouwing

Achtergrond

Aanvankelijk was de perceptie dat de respiratoire mechanica van patiënten met COVID-19 gerelateerd hypoxemisch falen in de vroege fase van beademing mogelijk is anders dan van patiënten met *acute respiratory distress syndrome* (ARDS) niet gerelateerd aan COVID-19 ('non-COVID ARDS', Gattinoni, 2020). Inmiddels is gebleken dat de respiratoire mechanica vergelijkbaar is tussen deze twee syndromen (Vandenbunder, 2021). Desondanks bestaat de vraag of het optimale PEEP niveau anders is bij COVID-19 gerelateerd hypoxemisch falen. Dit andere benodigde PEEP niveau kan effect hebben op daarmee samenhangende positieve en negatieve effecten van PEEP (Grasso, 2020). De positieve effecten van een adequaat ingestelde PEEP zijn onder andere een betere compliantie, betere oxygenatie en daarmee een reductie van de pulmonale vaatweerstand. Een belangrijk negatief effect van PEEP niveau is hyperinflatie, wat leidt tot een inflammatoire reactie in de betreffende longgebieden en zo een toename van longschade (*Ventilator-induced lung injury*, VILI). Daarnaast kan hoge intrathoracale druk de afterload van de rechter ventrikel verhogen. Samen kan dit leiden tot een verhoogde shear stress, hypoxemie en een verminderde orgaanperfusie. Een negatief effect van een te laag PEEP niveau is het collaberen van longweefsel, wat eveneens leidt tot een verminderde compliantie en oxygenatie en een verhoogde pulmonale vaatweerstand. Zowel een te hoog als een te laag PEEP niveau hebben dus negatieve consequenties, daarom dient gezocht te worden naar het optimale PEEP niveau. Een eenduidige definitie van hoge PEEP en lage PEEP is niet voorhanden, daarom wordt voor de literatuur search ongespecificeerde hogere en lagere PEEP gebruikt.

Conclusies / Summary of Findings

- GRADE	It was not possible to draw conclusions or grade the level of evidence for any outcome, due to the absence of randomized clinical trials comparing high and low PEEP during invasive mechanical ventilation in patients with COVID-19.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the (un)favorable effects of high positive end-expiratory pressure (PEEP) compared low PEEP during invasive mechanical ventilation in patients with COVID-19?

P: patients with COVID-19 undergoing mechanical ventilation

I: high PEEP

C: low PEEP

O: mortality in ICU, in-hospital mortality, ICU length of stay, hospital length of stay, ventilator-free days

Relevant outcomes

The guideline development group considered outcome mortality as a critical outcome measure for decision making; and outcomes ICU length of stay, hospital length of stay, ventilator-free days as important outcome measures for decision making.

The working group did not define high and low PEEP a priori, but followed the definitions used in literature. For the outcomes, the working group used the definitions used in the studies.

As minimal clinically (patient) important differences, the working group used 3% for mortality (risk ratio, RR), 1 day for ICU length of stay and ventilator-free days, 3 days for hospital length of stay, 10% for continuous outcomes and 0.5 for standardized mean differences.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until January 31, 2022. The detailed search strategy is depicted under the Methods tab. The systematic literature search resulted in 469 hits. Studies were selected based on the following criteria: randomized clinical trials comparing high and low PEEP during invasive mechanical ventilation in COVID-19 patients. Based on title and abstract screening, all studies were excluded (see the table with reasons for exclusion under the Methods tab).

Results

No RCTs conform the PICO were identified.

Verantwoording

Laatst beoordeeld : 09-02-2023

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Cardiovasculaire complicaties en cardiovasculaire ziekten covid-19

Waar gaan deze richtlijnmodules over?

Deze richtlijnmodules geven aanbevelingen over het in kaart brengen van cardiale schade bij in het ziekenhuis opgenomen COVID-19 patiënten, prognostische factoren voor het risico op een ernstig ziektebeloop en overlijden bij COVID-19 patiënten met cardiovasculaire risicofactoren of cardiale ziekte en het gebruik van medicatie die de ACE-2 expressie beïnvloedt bij patiënten die een COVID-19 infectie doormaken.

De volgende modules zijn uitgewerkt:

1. Omvang van cardiale schade bij in het ziekenhuis opgenomen COVID-19 patiënten
2. Prognostische factoren voor uitkomst bij COVID-19 patiënten met cardiovasculaire risicofactoren of cardiale ziekte
3. Effect van medicatie die ACE-2 expressie beïnvloedt op uitkomst bij COVID-19 patiënten

Voor wie is deze richtlijn bedoeld?

Deze richtlijn is bedoeld voor ieder specialisme dat betrokken is bij COVID-19 patiënten met cardiovasculaire risicofactoren of cardiale ziekte die opgenomen zijn op de verpleegafdeling of de IC.

Voor patiënten

Als u een ziekte van hart en bloedvaten heeft of heeft gehad, heeft u meer kans om ernstig ziek te worden of te overlijden door corona. Deze modules beschrijven aspecten die belangrijk zijn voor patiënten met een ziekte van hart en bloedvaten die een corona infectie doormaken, zoals hoe schade aan het hart in kaart kan worden gebracht en of het gebruik van bepaalde medicijnen voor uw hart of bloedvaten veilig gebruikt kan worden tijdens een corona infectie.

Zie ook de informatie op [Thuisarts.nl](https://www.thuisarts.nl):

<https://www.thuisarts.nl/corona/ik-heb-corona-en-krijg-behandeling-in-ziekenhuis>

Hoe is de richtlijn tot stand gekomen?

Op initiatief van de Federatie Medisch Specialisten is begin 2021 gestart met de ontwikkeling van de richtlijn COVID-19. Deze richtlijn beschrijft de infectiepreventie, diagnostiek, behandeling en revalidatie en nazorg voor alle COVID-19 (verdachte) patiënten. Deze richtlijn is deels gebaseerd op eerder gepubliceerde leidraden over COVID-19. In het voorjaar van 2021 is de leidraad 'Cardiovasculaire complicaties en cardiovasculaire ziekten COVID-19' ontwikkeld op initiatief van de Nederlandse Vereniging voor Cardiologie (NVVC). Daarnaast is er aandacht besteed aan het patiëntenperspectief door het meelezen van de patiëntenvereniging Harteraad. De verkregen input is meegenomen bij het opstellen van de module.

Omvang van cardiale schade bij in het ziekenhuis opgenomen COVID-19 patiënten

Uitgangsvraag

How often and in what extent do admitted COVID-19 patients have signs of cardiac injury as defined according to the Fourth Universal Definition of Myocardial Infarction? And if so, what is the outcome of the non-ischemic injury and ischemic (type 1 and 2) infarction patients?

Aanbeveling

Overweeg cardiale markers (troponine) te bepalen bij opname van een COVID-19 patiënt en indien afwijkend deze te vervolgen conform de 'Aanbeveling voor vroege detectie cardiale schade bij COVID-19 infectie' van de NVVC.

Verricht afhankelijk van het biochemische verloop aanvullende cardiale diagnostiek (anamnese, ECG en beeldvorming) tijdens opname of daarna.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïnccludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.

De aanwezigheid van myocardiale schade varieerde in de verschillende studies tussen 9,6% en 46,3%. Van alle geïnccludeerde patiënten in de pooled risk ratio van cardiale schade in relatie tot mortaliteit had 40% myocardiale schade. In de pooled risk ratio in relatie tot IC opname had 25% myocardiale schade. Grofweg kan gesteld worden dat minimaal een kwart van de patiënten met COVID-19 die opgenomen moeten worden in het ziekenhuis myocardiale schade heeft. Patiënten met myocardiale schade hebben een hogere mortaliteit en moeten vaker op de IC worden opgenomen. Dit is een klinisch relevant effect voor een grote patiëntenpopulatie.

Slechts 2 van de geïnccludeerde studies beschreven opname duur als uitkomstmaat, een studie vond een significant verschil tussen patiënten met en zonder myocardiale schade, de andere studie vond geen significant verschil. Op basis van deze resultaten kan hierover dan ook geen conclusie getrokken worden. De bewijskracht uit de literatuur search is laag tot zeer laag. Dit komt o.a. door het retrospectieve design van de geïnccludeerde studies en de mate van heterogeniteit. Echter laten wel alle geïnccludeerde studies, evenals de pooled risk ratios, het positieve effect van myocardiale schade op mortaliteit en IC opname zien. Daarnaast is het belangrijk te realiseren dat het literatuuronderzoek is uitgevoerd met de op 6 juli 2020 beschikbare gegevens. Na deze datum zijn er onderzoeken gepubliceerd die helaas niet meer konden

worden meegenomen in de analyse. Studies van latere datum met gegevens uit Azië en Europa ondersteunen ook de bevinding van het positieve effect van myocardiale schade op mortaliteit en IC opname, zoals onder andere blijkt uit studies van Cao (2020) en Stefanini (2020).

De conclusies van het literatuur onderzoek en ook recentere literatuur maken het daarom aannemelijk dat myocardiale schade een ongunstig effect heeft op het beloop van COVID-19 patiënten. Echter om dit met meer zekerheid te kunnen stellen is een grote prospectieve studie nodig.

Het meten van myocardiale schade door middel van laboratoriumdiagnostiek (cardiaal troponine) heeft geen nadelige effecten voor de patiënten aangezien dit meegenomen kan worden in het routinematige laboratoriumonderzoek dat gedurende een ziekenhuis opname plaats vindt.

De meeste data uit de literatuur search komt uit ziekenhuizen buiten Europa, meestal uit China, en vanuit regio's die zwaar getroffen zijn door de pandemie. Dit zou effect gehad kunnen hebben op de mate van myocardiale schade. Het is dan ook de vraag of de resultaten uit de literatuur search ook volledig van toepassing zijn op de Nederlandse populatie. In de meeste geïnccludeerde studies zijn de troponine waarden alleen bij opname bepaald. Hierdoor zijn mogelijk ook patiënten met een chronisch verhoogd troponine meegenomen. Onder andere bij patiënten met chronisch hartfalen, diabetes mellitus, pulmonale hypertensie en chronische nierziekten kan het troponine chronisch verhoogd zijn. Deze chronische comorbiditeiten zijn echter ook bekende risicofactoren voor een gecompliceerd beloop van COVID-19. Het is dan ook de vraag of in deze groep de hogere mortaliteit en IC opnames volledig kan worden toegeschreven aan nieuwe myocardiale schade door COVID-19 of dat de verhoogde troponine waarden het resultaat zijn deze chronische comorbiditeiten. Om onderscheid te kunnen maken tussen deze 2 patiëntgroepen is het van belang het troponine gedurende de opname te vervolgen om een rise and fall te kunnen detecteren. Evenwel is het belangrijk om onderscheid te maken tussen ischemische (type 1 en type 2 myocardiinfarct) en non-ischemische myocardi schade (acute en chronische myocardi schade tgv myocarditis, hartfalen en/of nierinsufficiëntie). Vanuit dat oogpunt is bij aanwezigheid van verhoogde troponine waarden het afnemen van een specifieke cardiale anamnese, het verrichten van ECG's en cardiale beeldvorming belangrijk om tot een specifiekere diagnose te komen.

CAPACITY

CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (<https://capacity-covid.eu/>). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524).

De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

In het prospectief opgezette CAPACITY II multicenter cohort onderzoek zal nader onderzoek verricht worden naar het optreden van cardiovasculaire complicaties bij COVID-19 en wat de korte en lange termijn gevolgen zijn. Vierhonderd COVID-19 patiënten met minimaal 4x UNL gestegen positieve troponine en/of nieuwe pathologische ECG afwijkingen en/of verdenking op cardiale aandoening binnen 24 uur na opname worden geïnccludeerd en volgens de 'Aanbeveling voor vroege detectie cardiale schade bij COVI-19 infectie' van de

NVVC vervolgd. Naast deze 400 patiënten met aanwijsbare cardiale betrokkenheid, worden ook 100 COVID-19 patiënten gevolgd die geen cardiale betrokkenheid hebben. Dit cohort dient als een controle groep. De follow-up belooft maximaal 10 jaar.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Patiënten met COVID-19 worden geadviseerd om, tijdens of na ziekenhuisopname, aanvullende cardiale diagnostiek zoals ECG en troponine bepaling te laten verrichten indien daar aanleiding toe is. Patiënten die opgenomen zijn geweest met COVID-19 dienen alert te zijn op klachten zoals symptomen van hartfalen die kunnen wijzen op cardiale restschade en die te bespreken met hun huisarts of medisch specialist.

Kosten (middelenbeslag)

De kosten van een troponine bepaling zijn zeer laag, € <10 (NZa, 2020). Daar tegenover staat dat het waardevolle informatie over de prognose van een patiënt kan geven, waardoor hoog risicopatiënten eerder opgespoord kunnen worden. De troponine waarden zouden gebruikt kunnen worden in risico stratificatie modellen voor triage van hoog risicopatiënten die bijvoorbeeld baat zouden kunnen hebben van vroege medicatie toediening. Dit zou op de langere termijn juist kosten kunnen besparen als dit tot kortere ziekenhuisopname zou leiden. Om hierin meer inzicht te verkrijgen is echter wel aanvullend onderzoek nodig. Er is nog veel onduidelijkheid t.a.v. het onderliggende mechanisme van de myocardiale schade. Dit zou kunnen berusten op non-ischemische oorzaken zoals virale myocarditis dan wel ischemische schade o.b.v. zowel een type I als II myocardinfarct. Om bij deze patiënten de juiste therapie in te kunnen zetten is aanvullende diagnostiek in de vorm van specifieke cardiale anamnese, ECG's en cardiale beeldvorming (echocardiografie, cardiale MRI en zo nodig coronair angiografie) nodig. Het standaard bepalen van troponine bij COVID-19 patiënten zal dan ook leiden tot een toename van aanvullende diagnostiek gedurende de opname. Dit geeft hogere kosten, echter als hierdoor eerder gestart kan worden met een geschikte interventie zoals een revascularisatie of het opstarten van hartfalen medicatie brengt dit uiteindelijk ook weer gezondheidswinst met zich mee.

Aanvaardbaarheid, haalbaarheid en implementatie

Er is geen kwantitatief of kwalitatief onderzoek gedaan naar de aanvaardbaarheid en haalbaarheid van de interventie. Echter het bepalen van cardiaal troponine kan routinematig worden meegenomen in de laboratoriumdiagnostiek gedurende de opname en brengt zeer lage kosten met zich mee. Dit zou daarom ook geen belemmering moeten vormen. Een nadeel zou echter kunnen zijn dat aan een verhoogd troponine ook consequenties gebonden moeten worden en aanvullend een cardiale anamnese, ECG en cardiale beeldvorming nodig is om het onderliggend mechanisme (myocarditis dan wel myocardiale ischemie) in specifieke patiënten te achterhalen om tijdig met een geschikte interventie te starten. Dit brengt hogere zorgkosten met zich mee en zou gevolgen kunnen hebben voor de wachtlijsten voor de betreffende beeldvorming in een ziekenhuis.

Om meer inzicht te verkrijgen in de onderliggende mechanismes van myocardiale schade is aanvullend prospectief onderzoek nodig waarbij standaard cardiale anamnese, ECG's en aanvullende cardiale beeldvorming wordt verricht bij COVID-19 patiënten met verhoogde troponine waarde. Dit kan helpen in de besluitvorming om aanvullende diagnostiek in te zetten bij patiënten met COVID-19 en myocardiale schade. Vanuit patiënt oogpunt zijn er voor het bepalen van troponine geen bezwaren te verwachten. Indien aanvullende beeldvorming noodzakelijk is zijn hier natuurlijk wel de risico's van het betreffende onderzoek

aan verbonden en moet hiervoor informed consent aan de patiënt gevraagd worden. Er is geen bezwaar in het kader van gezondheids gelijkheid, de betreffende onderzoeken/interventies zijn voor iedereen beschikbaar.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Ondanks de lage bewijskracht van de literatuur search, laten alle geïnccludeerde studies een slechtere uitkomst zien bij patiënten met COVID-19 en myocardiale schade. Mede gezien de lage kosten van een troponine bepaling en het feit dat dit gemakkelijk meegenomen kan worden in het routinematig laboratoriumonderzoek tijdens een ziekenhuisopname, adviseren wij om te overwegen bij iedere patiënt die wordt opgenomen met COVID-19 standaard troponine bepalingen te verrichten. Het is belangrijk om het troponine gedurende de opname op te volgen om een rise-and-fall te kunnen detecteren om onderscheid te kunnen maken met patiënten met een chronisch verhoogd troponine. Op deze manier kunnen hoog risicopatiënten tijdig worden opgespoord en kan triage plaats vinden van patiënten die mogelijk baat hebben bij vroegtijdig starten van therapie.

Het bepalen van troponine heeft tot gevolg dat bij een verhoogde waarde ook meer aanvullende cardiale diagnostiek noodzakelijk is. Dit brengt hogere zorgkosten en belasting voor de wachtlijsten met zich mee. Echter het vroegtijdig opsporen van hoog risicopatiënten en het onderliggende mechanisme van myocardiale schade maakte het mogelijk om eerder met een geschikte therapie te starten wat uiteindelijk ook weer gezondheidswinst op zou kunnen leveren.

Onderbouwing

Achtergrond

The paradigm that the presence of cardiovascular disease is a risk factor for severe COVID-19 and that COVID-19 can cause myocardial injury has recently been described. Questions remain whether and to what extent COVID-19 causes myocardial damage and whether myocardial injury is an important contributor of outcome with implications for management, like medication, imaging, long-term follow-up and perhaps situations where triaging patients is needed.

Conclusies / Summary of Findings

Mortality (crucial)

Low GRADE	Cardiac injury, defined as cTn elevation greater than 99th percentile, in COVID-19 patients could be associated with a higher risk of mortality. <i>Sources: Santoso, Lorente-Ros, Barman, Wei</i>

IC admission (important)

Very low GRADE	We are unsure if cardiac injury, defined as cTn elevation greater than 99th percentile, in COVID-19 patients is associated with IC admission. <i>Sources: Santoso, Lorente-Ros, Barman, Wei</i>

Hospital duration (important)

Very low GRADE	We are unsure if cardiac injury, defined as cTn elevation greater than 99th percentile, in COVID-19 patients is associated with the number of days of admission in the hospital. <i>Sources: Barman, Lorente-Ros</i>

Samenvatting literatuur

Description of studies

The aim of the review of **Santoso (2020)** was to explore the association between cardiac injury and mortality, the need for intensive care unit (ICU) care, acute respiratory distress syndrome (ARDS), and severe coronavirus disease 2019 (COVID-19) in patients with COVID-19 pneumonia. PubMed, SCOPUS, EuropePMC, ProQuest, and Cochrane Central Databases were searched. Search results were limited to 2020. All research articles in adult patients diagnosed with COVID-19 with information on cTnI, cardiac injury, and clinical grouping or outcome of the clinically validated definition of mortality, the need for ICU care, acute respiratory distress syndrome (ARDS), or severe COVID-19 were included. Articles other than original research (e.g., case report or series, review articles, letters to editor, editorials or commentaries), duplicate publication, and non-English articles were excluded. The search was finalized on March 29th 2020. A total of 13 studies were included. Four studies were not peer-reviewed. All studies were retrospective observational studies. Most of the included studies defined cardiac injury as cTnI above 99th percentile in which the troponine cut-off was different in the included studies. Some of the studies included in this review did not specify a definition for cardiac injury. Seven of the included studies reported on mortality and were included in a meta-analysis (Risk ratio M-H). Three studies were included in a meta-analysis considering the relation between cardiac injury and IC-admission (risk ratio M-H).

Barman (2020) aimed to delineate the prognostic importance of presence of concomitant cardiac injury on admission in patients with COVID-19 in Turkey. In this multi-center retrospective observational study, data of consecutive patients who were treated for COVID-19 between 20 March and 20 April 2020 were collected. Clinical characteristics, laboratory findings and outcomes data were obtained from electronic medical records. Acute cardiac injury was defined as high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG. In-hospital clinical outcome was compared between patients with and without cardiac injury. Total of 607 hospitalized patients with COVID-19 were included in the study. **Kuno (2020)** aimed to investigate whether cardiovascular disease or cardiac injury increased the risk of mechanical ventilation or mortality using the electronic medical records of Mount Sinai Health System in New York City. Kuno retrospectively analyzed a cohort of 8438 COVID-19 patients seen between March 1 and April 22, 2020. Mount Sinai health system combines 7 hospitals with more than 3800 beds and more than 410 ambulatory practices across metropolitan New York. Among 8438 patients, 54.7% of patients (N = 4616) were admitted to these hospitals. Analysis was performed on April 30th, 2020, which included patients who remained in the hospitals. Cardiac injury was defined as troponin I elevation which was defined as 99th percentile upper reference limit.

Lorente-Ros (2020) studied the effect of myocardial injury assessment on risk stratification of COVID-19 patients. In this observational study, a matched cohort of 112 patients was developed. After matching, an adequate comparability was shown by a decrease of the standardized differences to less than 20% for all covariates. Mortality was compared between patients with and without cardiac injury. Cardiac injury was

defined as cTnI levels greater than the 99th percentile of a healthy population.

Wei (2020) sought to characterize the prevalence and clinical implications of acute myocardial injury in a large cohort of patients with laboratory-confirmed COVID-19. Data of 103 consecutive patients with laboratory-confirmed SARS-CoV-2 infection admitted to the Public Health Clinical Centre of Chengdu and West China Hospital, Sichuan University, was collected between 16 January and 10 March 2020. Acute myocardial injury was defined by an cTnT value greater than the institutional upper limit of normal (14pg/mL). Outcomes of interest included death, admission to an intensive care unit (ICU), need for mechanical ventilation, treatment with vasoactive agents and classification of disease severity.

Table 1. describes the characteristics of the included studies.

Table 1 Study characteristics of included studies. It should be noted that the cardiac troponins (cTn) assays used in these studies differ in analytical characteristics, including their assessment of the upper reference limits, thereby limiting the direct comparability between studies.

Study	Study type	N	Country	Cardiac injury definition	Method	Outcome
Santoso, 2020	Systematic review	2389 (13 studies) Mortality: N= 1550 (7 studies) IC admission N=524 (3 studies)	Not reported except 'Most of the studies are from China'	highly sensitive cardiac troponin I (cTnI) above 99th percentile upper reference limit Moment of measurement: not reported	Odds ration meta-analysis (Mantel-Haenszel)	Mortality, IC admission
Barman, 2020	multi-center retrospective study	607	Turkey	high sensitivity cardiac troponin I serum levels above the 99th percentile upper reference limit, regardless of new abnormalities in ECG Moment of measurement: at hospital admission	Chi-square test was used to assess differences in categorical variables between groups. Student's t-test or Mann-Whitney U test was used to compare unpaired samples as needed. Cox regression model	Mortality, IC admission, hospital duration

Kuno, 2020	Retrospective study	8438 5320 in which troponin was measured	US	Cardiac injury was defined as troponin I elevation which was defined as 99th percentile upper reference limit Moment of measurement: not reported	RR, stratification for age groups	Mortality
Lorente-Ros, 2020	Matched retrospective cohort. After matching, an adequate comparability was shown by a decrease of the standardized differences to less than 20% for all covariates	707	Spain	cTnI levels greater than the 99th percentile upper reference limit Moment of measurement: at hospital admission	Multivariate Cox proportional hazards regression models	Mortality, IC admission, hospital duration
Wei, 2020	Prospective assessment of medical records	101	China	Acute myocardial injury was defined by an cTnT value greater than the institutional upper limit of normal (14pg/mL) Moment of measurement: at hospital admission	Student t-test or the Mann-Whitney U test to compare death for elevated cTn levels, Chi-square	Mortality, IC admission

Results

The included studies solely reported mortality (Santoso, Barman, Kuno, Lorente-Ros, Wei), IC-admission (Santoso, Barman, Lorente-Ros, Wei) and hospital duration (Barman, Lorente-Ros). Ventilation was also an outcome in some studies (Kuno, Lorente-Ros, Wei) but was not defined as days on ventilation but if ventilation was necessary. Therefore, this literature overview only reports on mortality, IC-admission and hospital duration.

1. Mortality

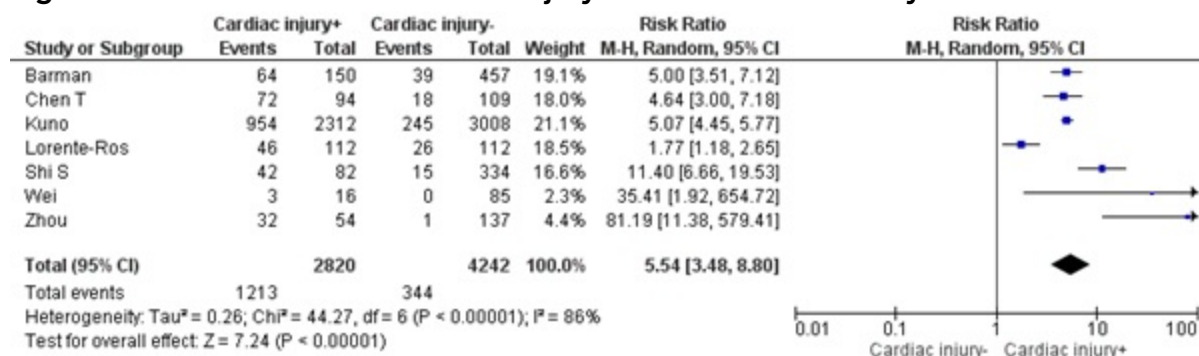
The systematic review of Santoso (2020) described 7 studies (of which 4 not peer reviewed) in which the

outcome mortality was studied. The meta-analysis of Santoso calculated a pooled risk ratio of 7.95 (95% CI 5.12-12.34). The heterogeneity (I^2) was 65%, meaning this may represent substantial heterogeneity. Barman (2020), Kuno (2020), Lorente-Ros (2020) and Wei (2020) also studied the outcome mortality in relation to cardiac injury. Barman (2020) and Lorente-Ros (2020) performed a univariate and multivariate regression analysis. In the study of Barman (2020) the univariate analysis (30 days) resulted in odds ratio (OR) of 7.97 (95% CI 5.03-12.64; $P < 0.001$). The multivariable regression model (30 day) resulted in OR 10.58 (95% CI 2.42-46.27; $P < 0.001$). In the multivariate model age, sex, hypertension, diabetes mellitus, CAD, smoking, COPD, creatinine, glucose, CRP and D-dimer ≥ 500 were taken into account in addition to cardiac injury. In the study of Lorente-Ros (2020) in the matched cohort all-cause mortality within 30 days was higher in those with cTnI elevation (41.1% vs. 23.2%; $p = 0.005$). The univariable regression model (30 days) resulted in Hazard Ratio (HR) of 4.355 (95% CI 3.112–6.093; $P < 0.001$). The Multivariable regression model (30 days) resulted in HR 1.716 (95% CI 1.182–2.492; $P = 0.005$). In the multivariable model sex, age, hypertension, RAAS inhibitors use, hematocrit, creatinine, D-Dimer, C-reactive protein and CCI were taken into account in addition to cardiac injury.

The study of Kuno (2020) resulted in an RR of 5.07 (95% CI 4.45-5.76) for mortality and the study of Wei (2020) calculated the difference between patients with and without cardiac injury that died. Patients with acute myocardial injury were older, with a higher prevalence of pre-existing cardiovascular disease and more likely to require ICU admission (62.5% vs 24.7%, $p = 0.003$), mechanical ventilation (43.5% vs 4.7%, $p < 0.001$) and treatment with vasoactive agents (31.2% vs 0%, $p < 0.001$). Log cTnT was associated with disease severity (OR 6.63, 95% CI 2.24 to 19.65), and all of the three deaths occurred in patients with acute myocardial injury.

A pooled risk ratio was calculated in which only the peer reviewed studies from the systematic review of Santoso (2020) and the results of Barman (2020), Kuno (2020), Lorente-Ros (2020) and Wei (2020) were included (figure 1.1). The pooled risk ratio of COVID-19 patients with cardiac injury in relation to mortality was 5.54 (95% CI 3.48 – 8.80). This means that COVID-19 patients with cardiac injury had a 5 times higher chance on mortality in comparison to a COVID-19 patient without cardiac injury. The I^2 was 86%, indicating that these studies might represented substantial heterogeneity.

Figure 1 Pooled risk ratio of cardiac injury in relation to mortality



2. IC admission (important outcome)

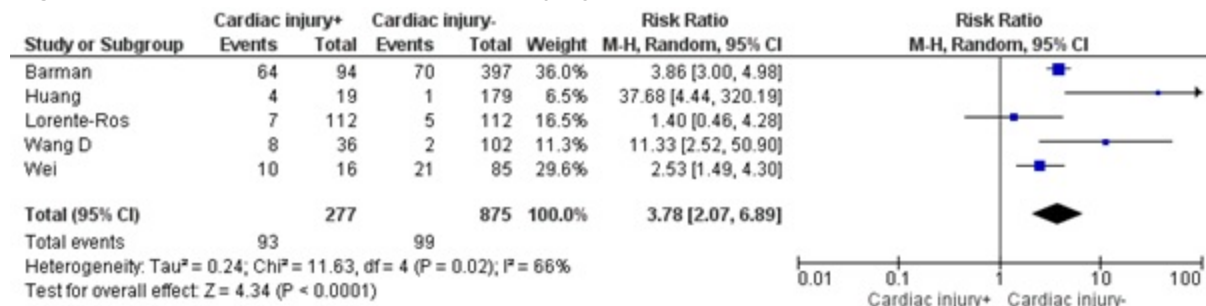
In the systematic review of Santoso (2020) three studies assessed the outcome IC admission and were included in a meta-analysis. Of the individual studies Barman (2020), Lorente-Ros (2020) and Wei (2020) assessed IC admission.

For IC admission the systematic review of Santoso shows a Pooled Risk Ratio (RR) of 7.94 (95% CI 1.51-41.78),

meaning that cardiac injury was associated with a higher need for IC admission in COVID-19 patients. The studies of Barman, Lorente-Ros and Wei compared the number of IC admission for COVID-19 patients with and without cardiac injury. The studies of Barman (72% vs 19%; $P < 0.001$) and Wei (62.5% vs 24.7%; $P = 0.003$) showed a significant difference between both groups. Lorente-Ros concluded that there was no significant difference between both groups (6.3% and 4.3%; $P = 0.527$). However, the number of patients requiring IC admission in this study were very small (7 and 5) what might have influenced the effect.

A pooled RR was calculated including only the peer reviewed studies from the systematic review of Santoso (2020) and the individual studies that assessed IC admission (figure 1.2). The pooled RR of COVID-19 patients with cardiac injury in relation to IC admission was 3.78 (95% CI 2.07-6.89). This means that COVID-19 patients with cardiac injury had a 3.8 times higher change of IC admission. The I^2 was 66%, indicating that these studies might represented substantial heterogeneity.

Figure 2 Pooled risk ratio of cardiac injury in relation to IC admission



3. Hospital duration (important outcome)

Barman (2020) reported a significant difference between patient with cardiac injury and without cardiac injury for hospital duration (Cardiac injury: 12 (5–14) days, no cardiac injury: 9 (4–12) days; $P < 0.001$). Lorente-Ros (2020) reported no significant difference between patient with cardiac injury and without cardiac injury for hospital duration (Cardiac injury: 11 (6 to 17) days, no cardiac injury: 9 (5 to 13) days; $P = 0.934$).

Level of evidence of the literature

The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, <http://www.gradeworkinggroup.org/>).

Mortality (crucial outcome)

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 2 levels because of risk of bias (retrospective design, correction for confounders often not applied) to 'low'.

IC admission (important outcome)

Starting with high level of evidence for observational studies in a prognostic studies, the level of evidence regarding the outcome measure IC admission was downgraded by 2 levels because of risk of bias (retrospective design, correction for confounders often not applied), by 1 level for indirectness (none of the

studies are performed in the Netherlands and each country can have different criteria for IC admission and IC admission may depend on IC capacity) by 1 level because of imprecision (wide confidence interval in study Santoso, few events in study of Lorente-Ros) to 'very low'.

Hospital duration (important outcome)

Starting with high level of evidence for prognostic studies, the level of evidence regarding the outcome measure hospital duration was downgraded with 1 level for inconsistency (both studies assessing hospital duration come to a different conclusion), 1 level for indirectness (the studies are performed in other European countries and each country may have their own criteria for hospital discharge), and 1 level for imprecision (only two studies included, low number of patients and follow up duration and number of patients lost to follow up unclear) to 'very low'.

Zoeken en selecteren

A review of the literature was performed to answer the following question:

What is the occurrence, extent and outcome of cardiac injury and myocardial infarction in admitted patients with COVID-19?

P: Admitted COVID-19 patients

I: Presence of evidence of elevated cardiac troponin values (cTn) – **either cTnT or cTnI** – with at least 1 value above the 99th percentile upper reference limit (URL).

C: Admitted COVID-19 patients without cardiac injury

O: Mortality, revascularization, IC-admission, days on ventilation, hospital duration, intervention (PCI, CABG, ICD implantation, Left and/or Right Ventricle Assist Device support), VA-ECLS, VV-ECLS.

-

Relevant outcome measures

Mortality and revascularization were considered as crucial outcome measures and IC-admission, days on ventilation, hospital duration, intervention (PCI, CABG, ICD implantation, Left and/or Right Ventricle Assist Device support), VA-ECLS, VV-ECLS important outcomes.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until July 6th 2020. The systematic literature search resulted in 484 hits. See search strategy for detail.

120 Studies were initially included based on title and abstract screening. After a second assessment in which the titles and abstracts of the 120 studies were assessed for inclusion based on the PICO, 26 studies were selected. Studies that described the underlying mechanism, described the wrong outcome, did not define the intervention in the right way, did not contain original data or were literature reviews but not systematic reviews were excluded. After reading the full text six papers were included (1 systematic review, 5 single studies). Since the search of the systematic review was performed on March 29, all studies published before that date were excluded (1 study). In total 5 papers (1 systematic review, 4 single studies) were included.

Results

Five studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Prognostische factoren voor uitkomst bij COVID-19 patiënten met cardiovasculaire risicofactoren of cardiale ziekte

Uitgangsvraag

In which proven COVID-19 patients with cardiovascular risk factors or underlying cardiovascular disease should one be alert to a poor outcome?

Aanbeveling

Beschouw patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen in de COVID pandemie als een risicogroep; patiënten met hartfalen hebben hierbinnen mogelijk een groter risico op overlijden. Zorgverleners en patiënten volgen in de vigerende adviezen en preventiemaatregelen vanuit de overheid en zorginstituten de aanwijzingen voor de risicogroepen.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïnccludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.

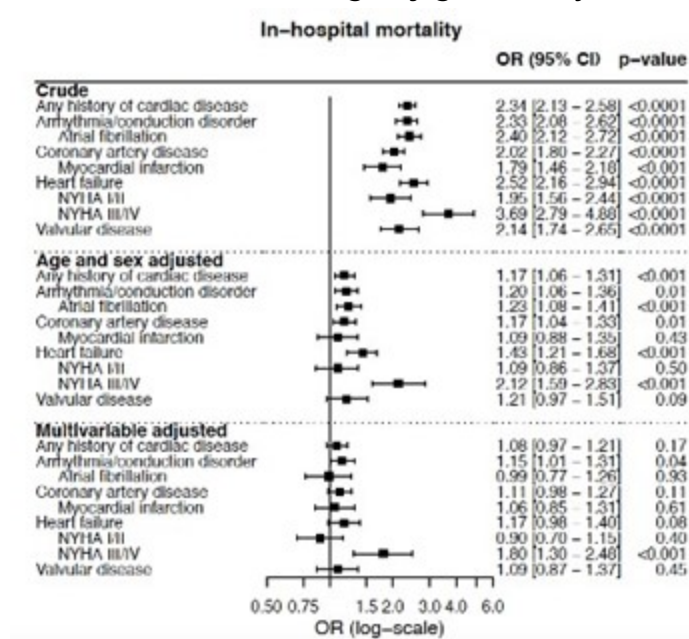
Op basis van de huidige literatuursamenvatting kunnen alleen conclusies worden getrokken waarin weinig vertrouwen wordt gegeven aan de correctheid van de schatting van het prognostisch effect van cardiovasculaire risico factoren of cardiovasculaire aandoeningen op mortaliteit. Hoewel op basis van de resultaten van de gerapporteerde modellen geconcludeerd zou kunnen worden dat BMI (gecorrigeerd voor leeftijd) statistisch gezien (klinische relevantie onbekend) een voorspeller zou kunnen zijn van mortaliteit, kan deze conclusie op dit moment niet worden ondersteund met bewijskracht vanuit de geselecteerde literatuur. De bewijskracht van de gevonden studies is zeer laag, onder andere door beperkingen in de methodologische opzet van de gevonden studies. Er is behoefte aan kwalitatief goed opgezette studies, welke gemaakte voorspellende modellen valideren in een Westerse populatie. In de literatuur werd daarom geen bewijs gevonden voor voorspellers die een rol zouden kunnen spelen bij mortaliteit in patiënten met COVID-19, wanneer wordt gecorrigeerd voor leeftijd.

Wanneer prognostische factoren kunnen worden vastgesteld, en deze gebruikt wensen te worden ten behoeve van klinische besluitvorming, maakt men gebruik van een beoordelingsmodel. Het is verstandig de voorspellende waarde van het te ontwikkelen beoordelingsmodel te optimaliseren door het te ontwikkelen model intern en extern te valideren en waar nodig te verbeteren. De effectiviteit van de toepassing van het ontwikkelde model wordt bij voorkeur getest in de praktijk door het effect op patiënt gerelateerde uitkomstmaten te meten alvorens het als standaard beoordelingsmiddel wordt ingezet.

CAPACITY

CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (<https://capacity-covid.eu/>). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524). De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

Figuur 1 Associaties tussen cardiale voorgeschiedenis en in-hospital mortaliteit uit de CAPACITY registry en data uit de LEOSS registry gezamenlijk (n=10712)



Een vergelijking van de basale kenmerken tussen patiënten met een cardiale voorgeschiedenis en patiënten zonder cardiale voorgeschiedenis laat zien dat patiënten met een cardiale voorgeschiedenis ouder zijn en meer cardiale risicofactoren en co-morbiditeit hebben.

De opnameduur op de Intensive Care en in het ziekenhuis zijn voor beide groepen vergelijkbaar. Patiënten met een cardiale voorgeschiedenis ontwikkelen vaker een acute nierinsufficiëntie tijdens de ziekenhuis opname en hebben vaker nierfunctiestoornissen in de voorgeschiedenis. In de vergelijking valt op dat een groter deel van de patiënten met een cardiale voorgeschiedenis komt te overlijden tijdens een ziekenhuisopname vanwege COVID-19 infectie.

Leeftijd, geslacht en algemene "frailty" lijken een belangrijke voorspellende waarde te hebben.

Preliminare resultaten van Nederlandse data uit de CAPACITY registry geven aan dat bij patiënten met een cardiale co-morbiditeit, hartfalen geassocieerd lijkt te zijn met een verhoogd risico op mortaliteit

gedurende de opname. Analyse van gecombineerde data (n= 10712) uit de CAPACITY registry en data uit de LEOSS registry (Lean European Open Survey on SARS-CoV-2 infected patients; dit is een multicenter prospectieve cohort studie met als primaire doel het identificeren van onafhankelijke predictoren voor uitkomst bij patiënten gediagnosticeerd met SARS-CoV2) laat zien dat er bij patiënten met een cardiale co-morbiditeit, na adjusteren voor leeftijd, geslacht, BMI, hypertensie, CKD, COPD en diabetes, een significante associatie bestaat tussen NYHA III/IV hartfalen en in-hospital mortaliteit.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Aan patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen kan meegegeven worden dat zij in de COVID-pandemie de aanwijzingen vanuit de overheid, zorgverleners en zorginstellingen over preventieve maatregelen en testindicaties volgen die betrekking hebben op de risicogroepen.

Kosten (middelenbeslag)

Niet van toepassing

Aanvaardbaarheid, haalbaarheid en implementatie

De aanbeveling is aanvaardbaar en haalbaar aangezien de COVID-infectie nadrukkelijk aandacht heeft en krijgt vanuit de overheid en zorgverleners. In de landelijke adviezen wordt expliciet aandacht besteedt aan de risicogroepen.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen zijn een kwetsbare groep op het gebied van infectieziekten. Er zijn geen aanwijzingen gevonden dat dit in de COVID-epidemie anders ligt. Overtuigende bewijskracht voor het effect van cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen op mortaliteit en ernst van het ziektebeloop bij COVID-19 infectie ontbreekt in de samengevatte literatuur. Echter, de aanwijzingen uit de CAPACITY registry dat patiënten met een cardiale voorgeschiedenis ouder zijn en meer co-morbiditeit hebben, dat leeftijd en frailty belangrijke voorspellers van mortaliteit zijn en dat meer patiënten met een cardiale voorgeschiedenis overlijden aan COVID-19 dan patiënten zonder cardiale voorgeschiedenis, worden als belangrijk gezien in het identificeren van deze patiëntengroep als een risicogroep. Derhalve wordt geadviseerd om de patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen in de COVID-epidemie te beschouwen als risicogroep en de daarvoor vigerende adviezen en preventiemaatregelen te volgen. Bij patiënten met cardiale co-morbiditeit lijkt vooral hartfalen (NYHA III/IV) geassocieerd met mortaliteit. Er zijn momenteel echter onvoldoende aanwijzingen gevonden die voor specifieke risicofactoren of aandoeningen aanzetten tot extra maatregelen bovenop de hiervoor genoemde.

Onderbouwing

Achtergrond

De COVID-19 pandemie roept wereldwijd diverse vragen op bij zorgverleners, onderzoekers en patiënten. Patiënten met cardiovasculaire risicofactoren en/of cardiovasculaire aandoeningen zijn een kwetsbare groep op het gebied van infectieziekten. Dit is onder meer te verklaren door de effecten van de diverse cardiovasculaire risicofactoren op de immunologische functie en de betrokkenheid van het immuunsysteem

bij het ontstaan van cardiovasculaire aandoeningen. Kennis over het risico op een ernstig ziektebeloop en overlijden bij deze groep patiënten is van belang voor een passende response op het gebied van voorzorgsmaatregelen, monitoring en therapie. Het tempo waarin de pandemie zich voltrekt, de globale verschillen in opname criteria, het ontbreken van voldoende testcapaciteiten en het ontbreken van systematische datacollectie zijn van invloed op de beschikbaarheid en kwaliteit van wetenschappelijke literatuur die inzicht kan verschaffen in de prevalentie van cardiovasculaire risicofactoren en cardiovasculaire aandoeningen bij COVID-19 patiënten. Gegeven het hiervoor genoemde is het zinvol om met regelmaat een kritische selectie te maken van beschikbare literatuur over de voorspellende waarde van cardiovasculaire risicofactoren en cardiovasculaire aandoeningen op het ziektebeloop en mortaliteit van COVID-19 patiënten en door middel van passende analyse modellen de data te doorgronden.

Conclusies / Summary of Findings

Mortality predicted by prognostic factors measured during hospital stay

Very low GRADE	We are unsure whether Body Mass Index is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Cummings, 2020; Giacomelli, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020</i>
Very low GRADE	We are unsure whether smoking is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Klang, 2020; Palaiodimos, 2020; Petrilli, 2020</i>
Very low GRADE	We are unsure whether hypertension is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Cummings, 2020; Gao, 2020; Klang, 2020; Petrilli, 2020</i>
Very low GRADE	We are unsure whether diabetes is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Cummings, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020</i>
Very low GRADE	We are unsure whether coronary artery disease or congestive heart failure is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Chen, 2020; Cummings, 2020; Klang, 2020; Palaiodimos, 2020; Petrilli, 2020</i>

Very low GRADE	We are unsure whether cerebrovascular disease is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Chen, 2020; Wang, 2020</i>

Very low GRADE	We are unsure whether heart failure is a predictor of mortality in COVID-19 patients admitted to hospital, adjusted for age. <i>Sources: Klang, 2020; Palaiodimos, 2020; Petrilli, 2020</i>

- GRADE	We cannot conclude which other cardiovascular risk factors, cardiovascular disease or cardiovascular history can predict mortality in COVID-19 patients due to lack of studies testing multivariable models taking age into account.

Hospital admission predicted by prognostic factors measured during hospital stay

- GRADE	We cannot conclude which cardiovascular risk factors, cardiovascular disease or cardiovascular history can predict hospital admission in COVID-19 patients due to lack of studies testing multivariable models taking age into account.

Samenvatting literatuur

Description of studies

Chen (2020), Giacomelli (2020) and Wang (2020) measured candidate factors during hospital stay and measured mortality outcome as endpoint. Cummings (2020), Gao (2020), Klang (2020) and Palaiodimos (2020) measured candidate factors during hospital stay and measured in-hospital mortality as endpoint. Petrilli (2020) measured candidate factors during hospital stay and measured discharge to hospice or death among those admitted to hospital as endpoint. Multivariable models showing associations between predefined candidate prognostic factors and outcome were reported. One study (Chen, 2020) internally validated the risk factors by establishing a nomogram based on the results of the multivariate analysis. It was decided to include unvalidated studies in the literature review for this outcome as well, as risk of bias of Chen (2020) was moderate.

A brief overview of study characteristics of the included studies is reported in table 1. Extended information about risk of bias is included in the and risk of bias table. It should be noted that populations, measurement of factors and selection methods of factors were not well reported in many studies.

Table 1 Study characteristics of included studies

Study	Population	N	Age Median (IQR)	Inclusion period	Follow- up	Method	Outcome

Chen, 2020	Hospitalized COVID-19 patients, from 575 hospitals; China	1590	Not reported	Admission to hospital until January 31, 2020 (startpoint of admission to hospital not reported)	Not reported	Multivariate Cox regression; included prognostic factors were selected based on univariable analyses; nomogram developed based on backward stepdown selection	Mortality
Cummings, 2020	Hospitalized COVID-19 patients ≥ 18 y, critically ill with acute hypoxaemic respiratory failure, 2 hospitals, USA	257	62 y (51-72)	Admission to hospitals between March 2 to April 1, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 28, 2020	Multivariate Cox regression; included prognostic factors were considered relevant to in-hospital mortality by the authors.	In-hospital mortality
Gao, 2020	Hospitalized COVID-19 patients, 1 hospital, China	2877	Not reported for total group	Admission to hospital between February 5 to March 15, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 1, 2020	Multivariable Cox proportional hazards model; reason of selection of included prognostic factors in multivariable model not described.	In-hospital mortality

Giacomelli, 2020	Hospitalized COVID-19 patients ≥ 18 y, 1 hospital, Italy	233	61 y (50-72)	Admission to hospital between February 21 and March 19, 2020; Candidate factors were measured during hospital stay (collected from medical records)	April 20, 2020	Multivariable Cox proportional hazard models; included prognostic factors were selected based on univariable analyses.	Mortality
Klang, 2020	Hospitalized COVID-19 patients ≥ 18 y, 5 hospitals, USA	3406	Not reported for total group	Admission to hospital between March 1 and May 17, 2020; Candidate factors were measured during hospital stay (collected from medical records)	Not reported	Multivariable logistic regression models; adjusted for age decile, male sex, CAD, CHF, HTN, DM, hyperlipidemia, CKD, history of cancer, smoking (past or present), BMI 30 – 40 kg/m ² , BMI ≥ 40 kg/m ² and race; included prognostic factors were selected based on univariable analyses; no validation reported	In-hospital mortality

Palaiodimos, 2020	Hospitalized COVID-19 patients, 1 hospital, USA	200	64 y (50-73.5)	Admission to hospital between March 9 to March 22, 2020; Candidate factors were measured during hospital stay (collected from medical records)	3-weeks follow-up: April 12, 2020	Multivariate logistic regression model; 3 models used (model 1: BMI and age; model 2: all the variables with significant univariate associations; model 3: variables of model 2 in addition to clinically significant variables which did not show a significant univariate association); no validation reported	In-hospital mortality
Petrilli, 2020	Admitted and not admitted to hospital COVID-19 patients, >260 outpatients office sites and 4 acute care hospitals, USA	5279 (2441 were admitted to the hospital)	Tested population: 54 y (38-66) Admitted population: 63 y (51-74)	Patients tested between March 1 and April 8, 2020; Candidate factors were measured during hospital stay (collected from medical records)	May 5, 2020	Multivariable logistic regression models; predictors selected based on previous published literature and clinical experience of authors of patients with COVID-19.	Inpatient hospital admission, discharge to hospice or death among those admitted to hospital

Wang, 2020	Hospitalized COVID-19 patients >60 y, 1 hospital, China	339	69 y (65-76)	Admission to hospital between January 1 and February 6, 2020; Candidate factors were measured during hospital stay (collected from medical records)	4 weeks from the last admission	Multivariate Cox regressions; included prognostic factors were selected based on univariable analyses; no validation reported	Mortality

Results of graded studies

All studies reported models predicting mortality and Petrilli (2020) reported a model predicting hospital admission. Table 2 shows the reported model design.

Table 2 Reported prognostic models for mortality

Study	Mortality n/N (%)	Outcome(s)	Included prognostic factors
Chen, 2020	50/1590 (3.1%)	Mortality	Age; Coronary heart disease; Cerebrovascular disease; Dyspnea; Procalcitonin; Aspartate aminotransferase; Total bilirubin; Creatinine
Cummings, 2020	101/257 (39.0%)	Time to in-hospital mortality from hospital admission	Age; Sex; Symptom duration before hospital presentation; Hypertension; Chronic cardiac disease; COPD; Diabetes; IL-6 concentrations; D-dimer concentrations
Gao, 2020	56/2877 (1.9%)	All-cause mortality during hospitalization	Hypertension; Age; Sex; Diabetes; Myocardial infarction; Treatment by percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG); Renal failure; Chronic heart failure; Asthma; COPD; Stroke
Giacomelli, 2020	48/233 (20.6%)	Mortality (censoring date April 20, 2020)	Age; Sex; Obesity; being treated with ≥ 1 anti-hypertensive agent; Disease severity; Presence of anemia; Lymphocyte count; D-dimer; C-reactive protein; Creatinine; Creatinine kinase
Klang, 2020	1136/3406 (33.4%)	In-hospital mortality	Age; Sex; Comorbidities (CAD, CHF, HTN, DM, hyperlipidemia, CKD, cancer); Obesity; Smoking status
Paladaiomidos, 2020	48/200 (24%)	In-hospital mortality	Age; BMI; Heart failure; Coronary artery disease; Diabetes; Chronic kidney disease or end-stage renal disease; COPD; current or former smoker
Petrilli, 2020	665/2741 (24.3%)	1) Admission to hospital 2) Mortality (only admitted patients in analysis)	Age; BMI; Sex; Week; Ethnicity; Smoking status; Coronary artery disease; Heart failure; Hypertension; Diabetes; Asthma or COPD; Chronic kidney disease; Cancer
Wang, 2020	65/339 (19.2%)	Mortality	Age; Cardiovascular disease; Cerebrovascular disease; COPD

Abbreviations: CAD, Coronary artery disease; CHF, Congestive heart failure; CKD, Chronic kidney disease; HTN, hypertension; DM, Diabetes mellitus; BMI, Body mass index.

Mortality predicted by prognostic factors measured during hospital stay

As reported models had different outcome measures and included factors were different, results could not be pooled. Because models were unvalidated, only results regarding factors that were included in at least two studies will be discussed. Table 3 shows relevance of reported associations for mortality.

Table 3 Relevance of prognostic factors for mortality

	Statistically significant								
	Chen	Cummings	Gao	Giacomelli	Klang	Klang	Palaiodimos	Petrilli	Wang
					Age≤50 y	Age>50 y			
Predictor	HR (95% CI)	HR (95% CI)	HR (95% CI)	HR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)	HR (95% CI)	HR 95% CI)
Age	Yes <65y: ref 65-74: 3.43 (1.24-9.5) ≥75: 7.86 (2.44-25.35)	Yes Per 10y: 1.39 (1.29-1.57)	Yes Per year: 1.06 (1.04-1.09)	Yes Per 10y: 2.08 (1.48-2.92)	Yes Per 10y: 3.0 (1.9-4.8)	Yes Decile: 1.7 (1.6-1.8)	Yes Quartiles: 1.73 (1.13-2.63)	Yes 19-44y: ref 45-54: 1.12 (0.80-1.60) 55-64: 2.04 (1.50-2.80) 65-74: 2.88 (2.46-4.80) ≥75: 3.46 (2.46-4.80))	Yes 1.86 (1.06-3.26)
BMI (kg/m ²)	-	No <40: ref ≥40: 0.76 (0.4-1.47)	-	Yes <30: ref ≥30: 3.04 (1.42-6.49)	Yes <30: ref 30-40: 1.1 (0.5-2.3) ≥40: 5.1 (2.3-11.1)	Yes >30: ref 30-40: 1.1 (0.9-1.3) ≥40: 1.6 (1.2-2.3)	Yes 25-34: ref <25: 1.37 (0.52-3.64) ≥35: 3.78 (1.45-9.83)	Yes <25: ref 25-30: 0.91 (0.74-1.11) 30-40: 1.02 (0.82-1.27) ≥40: 1.41 (0.98-3.02) Unknown: 1.85 (1.13-3.02)	-

Smoking	-	-	-	-	No 1.7 (0.8-3.8)	No 1.0 (0.8-1.2)	No 0.83 (0.37-1.87)	Yes Never: ref Former: 1.13 (0.93-1.37) Current: 0.90 (0.61-1.31) Unknown: 1.56 (1.26-1.93)	-
Hypertension (yes/no)	-	No 1.58 (0.89-2.81)	Yes 2.00 (1.13-3.54)	-	No 0.5 (0.2-1.1)	No 1.1 (0.9-1.3)		No 0.94 (0.76-1.16)	-
Diabetes (yes/no)	-	No 1.31 (0.81-2.10)	-	-	No 1.3 (0.7-2.6)	Yes 1.4 (1.2-1.7)	No 1.16 (0.55-2.44)	No 1.10 (0.93-1.31)	-
Coronary artery disease or congestive heart failure (yes/no)	-	Yes 1.76 (1.08-2.86)	-	-	-	-	-	-	-
Coronary artery disease (yes/no)	Yes 4.28 (1.14-16.13)	-	-	-	No 0.6 (0.2-2.1)	Yes 1.3 (1.1-1.6)	No 1.53 (0.54-4.34)	No 1.12 (0.92-1.36)	-
Cerebrovascular disease (yes/no)	Yes 3.1 (1.07-8.94)	-	-	-	-	-	-	-	No 1.38 (0.65-2.93)
Heart failure (yes/no)	-	-	Yes 3.3 (1.33-8.19)	-	Yes 4.0 (1.6-10.4)	No 1.0 (0.8-1.3)	No 1.43 (0.50-4.06)	Yes 1.77 (1.43-2.20)	-

Hospital admission predicted by prognostic factors measured during hospital stay

Hospital admission was only reported in the study of Petrilli (2020). Because the model was unvalidated and was included in only one study, the results regarding prognostic factors for hospital admission will not be discussed.

Level of evidence of the literature

The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, <http://www.gradeworkinggroup.org/>).

Mortality predicted by prognostic factors

Body Mass Index (BMI)

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, one included in the confidence interval) to 'very low'.

Smoking

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, one included in the confidence interval) to 'very low'.

Hypertension

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated) and 1 level for imprecision (wide confidence intervals, too many prognostic factors included in relation to number of events) to 'very low'.

Diabetes

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study) and by 1 level because of indirectness (studies are not validated)) and 1 level for imprecision (wide confidence intervals and one included in the confidence interval) to 'very low'.

Coronary artery disease or congestive heart failure

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 level because of indirectness (studies are not validated) and by 1 level because of inconsistency of results to 'very low'.

Cerebrovascular disease

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 levels because of indirectness (studies are not validated), by 1 level because of inconsistency of results and by 1 level because of number of included patients (imprecision) to 'very low'.

Heart failure

Starting with a high level of evidence for prognostic studies, the level of evidence regarding the outcome measure mortality was downgraded by 1 level because of risk of bias (some patients were still under treatment at the end of the study), by 1 levels because of indirectness (studies are not validated), by 1 level because of inconsistency of results and by 1 level because of number of included patients (imprecision) to 'very low'.

Zoeken en selecteren

A review of the literature was performed to answer the following question:

Which independent prognostic factors (cardiovascular risk factors or cardiovascular disease) strongly predict a poor outcome of COVID-19 infection, independent of other factors?

P: All proven COVID-19 patients

I: Presence of one of the following prognostic factors: cardiovascular risk factors such as smoking, obesity, hypercholesterolemia, hypertension, diabetes (insulin resistance, non-alcoholic steatohepatitis), cardiovascular disease, cardiovascular history (arrhythmias, coronary artery disease, heart failure, valvular heart disease)

C: absence of the prognostic factors

O: mortality (crucial), IC-admission (crucial), hospital admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack)

T: admission to hospital, admission to ICU, during hospital stay, at home

S: in-hospital, pre-hospital

Confounder: age

Relevant outcome measures

Mortality and IC-admission were considered as critical outcome measures for decision making and the other outcomes as important outcomes for decision making.

A priori, the working group did not define the outcome measures listed above, but used the definitions used in the studies.

A priori, the working group did not define minimal clinically relevant differences for the outcome measures.

Prognostic research: Study design and hierarchy

For this research question, it is aimed to investigate multiple cardiovascular factors that might predict disease severity and mortality in patients with COVID-19. To investigate whether factors are predictive, a longitudinal relation between candidate prognostic factors (measured at T0) and outcome (measured at T1) has to be investigated. Often, prognostic factors are correlated with other factors (Foroutan, 2020). To describe the effect of single prognostic factors, these should be measured in relation to its confounders. Mostly, important confounders can be predefined. Only models including all predefined confounders and measuring longitudinal associations between candidate predictors and outcome can be taken into account. When multiple factors are investigated, multivariable models predicting outcome are developed and will be used as a tool for clinical decision making.

When reviewing literature, there is a hierarchy in quality of individual studies. Preferably, models for clinical

decision making show the efficacy of using multivariable models in healthcare. In this way, they are most helpful to decide which factors should be used in clinical practice. Differences in clinical decision making according to the developed model and the effect on patient related outcome should be measured after sufficient follow-up periods (Moons, 2008). If such studies are not available, studies validating the effects of developed prognostic multivariable models in other samples of the target population (external validation) are preferred as there is more confidence in the results of these studies compared to not externally validated studies. Most samples do not completely reflect the characteristics of the total population, resulting in deviated associations, possibly having consequences for conclusions. Studies validating prognostic multivariable models internally (e.g. bootstrapping or cross validation) or studies reporting unvalidated prognostic multivariable models can be used to answer the research question as well, but downgrading the level of evidence is obvious due to risk of bias and/or indirectness as it is not clear whether models perform sufficient in target populations. Due to the low confidence in the results of externally unvalidated models, specific results regarding factors of interest reported in such models will be described only if factors have been used in at least two multivariable models/studies. Univariable prognostic models (or multivariable prognostic models not taking confounders into account) cannot be graded as confidence in these models is too low.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 9-6-2020. The systematic literature search resulted in 567 hits. See search strategy for detail. No studies investigating the impact of a multivariable cardiovascular prognostic model on healthcare regarding mortality, IC-admission, hospital admission, length of stay and/or thromboembolic complications were found. Studies developing and/or validating a multivariable prognostic model were selected based on the following criteria: systematic reviews, randomized controlled trials (RCTs) and observational studies (cohort studies) assessing the longitudinal relation between cardiovascular risk factors (smoking, obesity, hypercholesterolemia, hypertension, diabetes), cardiovascular disease and cardiovascular history (measured at hospital admission/during hospital stay), with mortality, IC-admission, hospital admission, length of stay, thromboembolic complications (measured at endpoint) in proven COVID-19 patients. Age was considered as confounder that had to be included in the multivariable models.

45 studies were initially selected based on title and abstract screening. After reading the full text, 37 studies were excluded (see the table with reasons for exclusion under the tab Methods), and 8 studies were included.

Some systematic reviews evaluated the association between cerebrovascular, cardiovascular disease, diabetes mellitus or hypertension and poor outcome in patients with COVID-19, for example Huang (2020), Li (2020), Lippi (2020), Pranata (2020a), Pranata (2020b) and Zheng (2020). These systematic reviews were not included, because associations were calculated without taking any confounders into account.

Results

Eight studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Effect van medicatie die ACE-2 expressie beïnvloedt op uitkomst bij COVID-19 patiënten

Uitgangsvraag

What is the effect of medication that influence ACE-2 expression (ACEi, ARBs, NSAIDs and thiazolidinediones) on the outcomes of COVID-19?

Aanbeveling

Staat of ontraad ACEi/ARBs niet bij mensen die een COVID-19 infectie doormaken ongeacht ernst van de infectie, anders dan om acute hemodynamische redenen, acuut ernstig nierfunctieverlies of ernstige nierinsufficiëntie.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

De kwaliteit van het bewijs van de geïnccludeerde studies is overwegend laag tot zeer laag. De GRADE systematiek is gevolgd om de kwaliteit van het bewijs te beoordelen. Deze is hier dan ook gevolgd. In een nieuwe situatie (zoals COVID) is het logisch dat de meeste studies nog niet kunnen voldoen aan de strenge eisen die aan studies van hoge kwaliteit worden gesteld. De GRADE methodiek zet de kwaliteit van het bewijs echter af tegen de best mogelijke kwaliteit en niet tegen de best mogelijke kwaliteit in de huidige situatie. De GRADE systematiek geeft het vertrouwen weer in de schatting van het effect van een interventie. Wanneer de modules en de search worden geüpdate zijn er hopelijk studies van betere kwaliteit beschikbaar en kan het niveau van de kwaliteit van het bewijs hierop worden aangepast.

In deze literatuursamenvatting is het effect van het gebruik van ACEi, ARBS, NSAIDS en thiazolidinediones van COVID-19 patiënten onderzocht op de uitkomstmaten mortaliteit, ic opname, ziekenhuisopname, verblijfsduur, ventilatie en tromboembolische complicaties. Mortaliteit was gedefinieerd als kritische uitkomstmaat. De literatuur laat zien dat er geen associatie is tussen gebruik van ACEi/ARBS (gecombineerd of los van elkaar) met mortaliteit voor zowel de overall groep (waarin gebruikers met niet gebruikers worden vergeleken) als de subgroep met alleen hypertensieve patiënten. De kwaliteit van het bewijs varieert van moderate (voor de overall groep waarin ACEi/ARBS gebruikers gecombineerd) tot zeer laag. Met betrekking tot NSAID gebruik is de kwaliteit van het wetenschappelijk bewijs zeer laag en kunnen geen conclusies voor de praktijk worden getrokken.

Voor de belangrijke uitkomstmaten was de kwaliteit van het bewijs laag tot zeer laag. Ook hier wijst het gebruik van het gebruik van ACEi, ARBS (zowel los als gecombineerd) en thiazolidinediones op geen of nauwelijks associatie met de belangrijke uitkomstmaten.

Er zijn nauwelijks studies waarin gebruik van ACEi, ARBs werd geassocieerd met hoger risico op slechte uitkomst, een van de weinige (Sulcuk et al) was een zeer kleine studie. Over het algemeen was er een zwakke associatie met betere uitkomsten bij gebruik van deze middelen (zie figuur 1 en 2). Dit sluit nagenoeg uit dat deze middelen een negatief effect hebben op het beloop van een COVID-19 infectie. Het toont niet aan dat ze beschermend zijn, maar een beschermend effect kan niet worden uitgesloten. Herhaaldelijk uitsluiten van associatie met nadelige uitkomsten is wel in staat om de kans dat dat een dergelijk middel direct nadelige

effecten heeft als zeer onwaarschijnlijk te beoordelen. Kortom, er is sterk bewijs voor de afwezigheid van een relatie tussen gebruik van ACEI, ARBs en slechtere uitkomsten. Er is geen sterk bewijs voor de beschermende effecten van deze middelen, maar dit kan ook niet worden uitgesloten.

CAPACITY

CAPACITY is een internationale registratie van patiënten met COVID-19 op basis van het ISARIC WHO CRF, aangevuld met informatie over specifieke cardiovasculaire parameters (<https://capacity-covid.eu/>). CAPACITY is in het voorjaar van 2020 gestart en bevat gegevens van 13034 patiënten uit 13 landen, afkomstig van 79 registrerende centra. CAPACITY bevat omvangrijke informatie over patiënten met COVID, omdat ongeveer 40% van de in Nederland opgenomen COVID19 patiënten in de registratie is opgenomen (n = 5524). De peer-reviewed publicatie van CAPACITY over het onderwerp van deze module is momenteel in voorbereiding. De resultaten van CAPACITY kunnen daarom nog niet worden meegenomen bij het literatuuronderzoek, maar bij de overwegingen worden wel de voorlopige resultaten van CAPACITY meegenomen. De peer-reviewed publicatie over het onderwerp van deze module wordt binnenkort verwacht en bij een update van de module zal de publicatie in het literatuuronderzoek worden meegenomen.

De eerste analyses van de CAPACITY data zijn in lijn met bovengenoemde bevindingen. Daarbij lijken nog zeer voorlopige analyses te suggereren dat staken van juist meer krachtige ARBs geassocieerd is met slechtere uitkomsten ook na correctie voor confounders. Deze analyses moeten nog definitief worden bevestigd.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Patiënten die een behandeling met ACEI/ARBs krijgen vinden complete en eenduidige informatievoorziening belangrijk, o.a. over de veiligheid en risico's van de behandeling.

Kosten (middelenbeslag)

De genoemde middelen zijn veelal reeds uit patent en daarmee generiek verkrijgbaar en zeer goedkoop (<1 euro per dag). De aanbevelingen die hier gedaan worden hebben vrijwel geen effect op kosten.

Aanvaardbaarheid, haalbaarheid en implementatie

Continueren van antihypertensiva bij patiënten met een ernstig verlopende infectieziekte zal in de dagelijkse praktijk discussie kunnen geven gezien de zorg voor te veel effect op de bedreigde bloeddrukregulatie. Daarom is uitdrukkelijk het advies om per geval te beoordelen of deze middelen doorgegeven kunnen worden, waarbij we hier herhalen dat indien klinisch wordt ingeschat dat deze worden verdragen het aanbeveling verdient ze niet te staken.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Er is geen relatie tussen gebruik ACEI en ARB en slechtere uitkomsten COVID-19 infectie. Dit is een sterk gegeven gezien meerdere studies deze associatie niet vinden op 1 kleine studie na. Eerder gebruik van ACE/ARBs lijkt geassocieerd met minder slechte uitkomsten van een ernstige COVID-19 infectie. Staken tijdens opname van ACE/ARBs in het kader van COVID-19 infectie is geassocieerd met slechtere uitkomsten. De gevonden associaties zijn zwak, echter met een redelijke effectgrootte. Het type bewijs is ook zwak (retrospectief).

Onderbouwing

Achtergrond

COVID-19 gebruikt het ACE-2 om de cel te infecteren. Dit ACE-2 breekt angiotensine II af. Angiotensine II verhoogt de bloeddruk. Medicijnen die worden gegeven tegen te hoge bloeddruk zoals ACE remmers of ARBs kunnen het niveau van ACE-2 verhogen. Er werd aanvankelijk gedacht dat veel ACE-2 gevoeliger zou maken voor COVID-19 omdat het immers de 'poort' is voor het virus. Echter, ACE-2 lijkt ook te beschermen tegen teveel angiotensine II, en teveel angiotensine II komt vaak voor in de long bij een door COVID-19 veroorzaakte longontsteking. Het is dus onduidelijk of medicijnen die ACE-2 verhogen of juist verlagen kwaad kunnen.

Conclusies / Summary of Findings

1. Mortality

1.1 Overall

Moderate GRADE	ACEI/ARBS use probably does not increase mortality. <i>Sources: Zhang (2020), Imam (2020), López-Otero (2020), Reynolds (2020)</i>

Low GRADE	The evidence suggests that ARBS use does not increase mortality. <i>Sources: Reynolds (2020), Mancía (2020) , Jung (2020) , Mehra (2020)</i>

Low GRADE	The evidence is uncertain about the effect of ACEI use on mortality. <i>Sources: Mancía (2020), Reynolds (2020), Bean (2020), Mehra (2020)</i>

Low GRADE	The evidence suggests that thiazolidinediones use does not increase mortality. <i>Sources: Reynolds (2020)</i>

Very low GRADE	The evidence is very uncertain about the effect of NSAIDS use on mortality. <i>Sources: Imam (2020)</i>

1.2 Hypertensive patients

Very low GRADE	ACEI/ARBS use may not increase mortality, but the evidence is very uncertain <i>Sources: Zhang (2020), Felice (2020), Gao (2020), Zhou (2020), Reynolds (2020), Selçuk (2020)</i>

Low GRADE	The evidence suggests that ARBS or thiazolidinediones use does not increase mortality. <i>Sources: Reynolds (2020), Mehra (2020)</i>

Very low GRADE	The evidence is very uncertain about the effect of ACEI use on mortality. <i>Sources: Reynolds (2020), Mehra (2020)</i>

2. IC admission

2.1 Overall

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS or ACEI use on IC admission. <i>Sources: Reynolds (2020), López-Otero (2020), Bean (2020), Rentsch (2020)</i>

Very low GRADE	ARBS use may have no effect on IC admission, but the evidence is very uncertain. <i>Sources: Reynolds (2020), López-Otero (2020)</i>

Low GRADE	The evidence suggests that thiazolidinediones use does not increase IC admission. <i>Sources: Reynolds (2020)</i>

2.2 Hypertensive patients

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS on IC admission <i>Sources: Reynolds (2020), Felice (2020), Selçuk (2020)</i>

Low GRADE	The evidence suggests that ARBS use, ACEI use, or thiazolidinediones use does not increase IC admission. <i>Sources: Reynolds (2020)</i>

3. Hospital admission

3.1 Overall

Low GRADE	The evidence suggests that ACEI/ARBS use, ARBS use, or ACEI use does not increase hospital admission. <i>Sources: López-Otero (2020), Rentsch (2020), Rossi (2020)</i>

3.2 Hypertensive patients

Very Low GRADE	ACEI/ARBS use may have no effect on hospital admission, but the evidence is very uncertain. <i>Sources: Felice (2020)</i>

4. Length of stay

4.2 Hypertensive patients

Very low GRADE	ACEI/ARBS may have no effect on length of stay, but the evidence is very uncertain. <i>Sources: Selçuk (2020), Zhou (2020)</i>

5. Ventilation

5.1 Overall

Low GRADE	The evidence suggests that ACEI/ARBS use, ACEI use or thiazolidinediones use does not increase ventilation. <i>Sources: Reynolds (2020), Jung (2020), Mancía (2020)</i>

Very Low GRADE	ARBS use may have no effect on ventilation, but the evidence is very uncertain. <i>Sources: Reynolds (2020), Mancía (2020), Jung (2020)</i>

5.2 Hypertensive patients

Very low GRADE	The evidence is very uncertain about the effect of ACEI/ARBS use on ventilation. <i>Sources: Gao (2020), Reynolds (2020), Felice (2020), Selçuk (2020)</i>

Low GRADE	The evidence suggests that ARBS use, ACEI use or thiazolidinediones use does not increase ventilation. <i>Sources: Reynolds (2020)</i>

6. Tromboembolic complications

6.1 Overall

Very low GRADE	ACE/ARBS use, ARBS use or ACEI use may have no effect on tromboembolic complications, but the evidence is very uncertain. <i>Sources: López-Otero, Jung</i>

Samenvatting literatuur

Description of studies

Zhang (2020) assessed the relationship between ACEI/ARB use and COVID-19 infection in a systematic review. A comprehensive search of the PubMed, Embase, and Cochrane Library databases was performed to identify all relevant articles published between Jan 1, 2020 and May 9, 2020. Observational studies that met all the following criteria were included:

(1) study design: case-control, case-crossover, self-controlled case series (SCCS) or cohort study; (2) antihypertensive treatment: ACEI/ARB use versus non-ACEI/ARB use; (3) outcomes: the incidence of COVID-19, critical cases, or death; (4) adequate data were used to extract the risk estimates if the adjusted data were not provided in the publication. Editorials, correspondences, conference abstracts and commentary articles were excluded. Twelve articles (case-control and cohort studies) involving more than 19,000 COVID-19 cases were included. Information on follow-up duration or the number of patients for whom no complete outcome data was available was not mentioned.

Mackay (2020) evaluated whether use of ACEIs or ARBs either increased risk for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection or was associated with worse COVID-19 disease outcomes, and the efficacy of these medications for COVID-19 treatment in a systematic review. MEDLINE (Ovid) and Cochrane Database of Systematic Reviews were searched from 2003 to 4 May 2020, with planned ongoing surveillance for 1 year; the World Health Organization database of COVID-19 publications and medRxiv.org through 17 April 2020; and ClinicalTrials.gov to 24 April 2020, with planned ongoing surveillance. Observational studies and trials in adults that examined associations and effects of ACEIs or ARBs on risk for SARS-CoV-2 infection and COVID-19 disease severity and mortality were included. Nineteen studies were included. Some of the included studies describe a composite outcome measure 'severe COVID-19'.

Felice (2020) investigated the association between chronic use of angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin II receptor blockers (ARBs) and COVID-19 related outcomes in hypertensive patients. A single center study was conducted on 133 consecutive hypertensive subjects presenting to the Emergency Department with acute respiratory symptoms and/or fever who were diagnosed with COVID-19 infection between 9th and 31st March 2020. All patients were grouped according to their chronic antihypertensive medications (ACEIs, N=40; ARBs, N=42; not on RAAS inhibitors, N=51).

Gao (2020) investigated if treatment of hypertension, especially with RAAS inhibitors, had an impact on the mortality of patients with COVID-19. Consecutive patients admitted to Huo Shen Shan Hospital (solely to the treatment of COVID-19, in Wuhan, China) from 5 February to 15 March 2020 were included. In total, 2877 consecutive hospitalized patients with confirmed COVID-19 were enrolled in the study. The median time from symptom onset to discharge (last follow-up) was 39 (30–50) days. There were 710/850 (83.5%) patients with hypertension taking antihypertensive medications. There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) treated with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors). For the outcome measures of interest the group of 710 patients was used, meaning that hypertensive patients treated with RAAS inhibitors were compared to hypertensive patients on taking antihypertensive medications other than RAAS inhibitors.

The medical history and blood pressure at admission did not differ significantly between the RAAS inhibitor-treated [RAASi (+)] and non-RAAS inhibitor-treated patients [RAASi (-)]. There were 14 patients who reported shivering at admission in the RAASi (-) cohort, compared with none in the RAASi (+) cohort. There were 183 (25.7%) patients treated with RAAS inhibitors and 527 (74.2%) with beta-blockers, CCBs, or diuretics (non-RAAS inhibitors).

Jung (2020) aimed to assess the associations between prior use of RAAS inhibitors and clinical outcomes among Korean patients with coronavirus 2019 (COVID-19). Among 5179 confirmed COVID-19 cases, 762 patients were RAAS inhibitor users and 4417 patients were nonusers. Relative to nonusers, RAAS inhibitor users were more likely to be older, male, and have comorbidities. Among 1954 hospitalized patients with COVID-19, 377 patients were RAAS inhibitor users and 1577 patients were nonusers.

López-Otero (2020) performed a single-center, retrospective, observational cohort study on 965 patients diagnosed with COVID-19 from 10 March to 6 April 2020. In total, 210 patients were under ACEI or ARB treatment at the time of diagnosis. 165 (78.57%) were taking them for more than 1 year. During the study period, 38 patients died (3.94%), of whom 35 (3.6%) had heart failure. The cohort of patients under ACEI/ARB was older (72.1 ± 13.2 vs 56.0 ± 20.5 ; $P < 0.01$) and had more cardiovascular risk factors (hypertension, diabetes, smoking, and dyslipidemia) and cardiovascular comorbidities (coronary artery diseases and ventricular dysfunction) than the cohort without ACEI/ARB. There were fewer women in the ACEI/ARB group (43.8% vs 59.5%; $P < 0.01$). Renal impairment and peripheral vasculopathy were also more prevalent in patients taking ACEI/ARB.

Selçuk (2020) aimed to determine the relation between the use of angiotensin converting enzyme inhibitors (ACE inh) and angiotensinogen receptor blockers (ARBs) and in-hospital mortality of hypertensive patients diagnosed with COVID-19 pneumonia. All patients were on ACE inh/ARBs or other antihypertensive therapy. In total, 113 hypertensive COVID-19 patients were included, of them 74 patients were using ACE inh/ARBs. During in-hospital follow up, 30.9% ($n = 35$ patients) of patients died.

Imam (2020) evaluated mortality predictors of COVID-19 in a large cohort of hospitalized patients in the US. Retrospective, multicenter cohort of inpatients diagnosed with COVID-19 by RT-PCR from March 1-April 1, 2020 was performed, and outcome data evaluated from March 1-April 17, 2020. Measures included demographics, comorbidities, clinical presentation, laboratory values, and imaging on admission. Primary outcome was mortality. Secondary outcomes included length of stay, time to death, and development of acute kidney injury in the first 48-hours. 1305 patients were hospitalized during the evaluation period. Mean age was 61.0 ± 16.3 , 53.8% were male and 66.1% was African-American. Mean BMI was 33.2 ± 8.8 kg/m². Median Charlson Comorbidity Index (CCI) was 2 (1-4), 72.6% of patients had at least one comorbidity, with hypertension (56.2%) and diabetes mellitus (30.1%) being the most prevalent. ACE-I/ARB use and NSAIDs use were widely prevalent (43.3% and 35.7% respectively). Mortality occurred in 200 (15.3%) of patients with median time of 10 (6-14) days.

Zhou (2020) aimed to explore the clinical characteristics of COVID-19 complicated by hypertension. A retrospective, single-center study was conducted in which 110 discharged patients with COVID-19 at Wuhan

Fourth Hospital in Wuhan, China, from January 25 to February 20, 2020 were included. All study cases were grouped according to whether they had a history of hypertension. Then, a subgroup analysis for all hypertensive patients was carried out based on whether to take ACEI or ARB drugs. The mean age of 110 patients was 57.7 years (range, 25–86 years), of which 60 (54.5%) were male patients. The main underlying diseases included hypertension [36 (32.7%)] and diabetes [11 (10.0%)].

Table 1 General study characteristics

Author (year)	Study type	Comments	N	Country	Outcome
Zhang (2020)	Systematic review and meta-analysis			Multiple	<i>Mortality</i>
Mackay (2020)	Systematic review	There is overlap between studies included in Zhang and Mackay. Mackay included two studies for mortality that are not included in Zhang. One of those papers is not peer-reviewed and the other is in Chinese so both cannot be used.		Multiple	<i>Mortality was assessed but not used, see comments, IC admission Hospital admission</i>
Felice, (2020)	Observational study		133	Italy	<i>Mortality, IC admission, Hospital admission, Ventilation</i>
Gao (2020)	Observational study		2877	China	<i>Mortality, Ventilation</i>
Imam (2020)	Observational study		1305	US	<i>Mortality</i>
Jung (2020)	Observational study		5179	Korea	<i>Mortality, Ventilation, Thromboembolic complications</i>
López-Otero (2020)	Observational study		965	Spain	<i>Mortality, IC admission, Hospital admission, Thromboembolic complications</i>
Selçuk (2020)	Observational study		113	Turkey	<i>Mortality, IC admission, Hospital admission, Ventilation, Length of stay</i>
Zhou (2020)	Observational study		110 (36 of which were used for the analysis of interest)	China	<i>Mortality, length of stay</i>

Results

The results were described for two different groups, an overall group in which all users were compared with

non-users and a group in which only hypertensive patients were included. Within each group a distinction was made between results for ACEi/ARBS use, ACEi use, ARBS use or NSAID use.

1. Mortality

1.1 Overall

1.1.1 ACEi/ARBS

We were unable to provide a pooled estimate for mortality since some studies did not provide the absolute number of events or used a composite outcome measure. Therefore, the results of each of the studies were described separately.

Zhang (2020) performed a meta-analysis to study the relation between ACEi/ARBS use and mortality. In this meta-analysis, all studies that assessed this relation were included, irrespective of the type of patients in the intervention (all patients using ACEi/ARBS or only hypertensive patients) and control group (all COVID-19 patients not on ACEi/ARBS, hypertensive patients not on ACEi/ARBS but on other or no blood pressure lowering medication). Overall, the risk of mortality in ACEi/ARB-exposed was similar to non-ACEi/ARB exposed COVID-19 patients (pooled OR 0.73; 95% CI 0.5-1.07; $P=0.11$) (figure 3.1).

Imam (2020) and López-Otero (2020) also studied the relation between ACEi/ARBS use and mortality between users of ACEi/ARBS and non-users. In a multivariate analysis both Imam and López-Otero reported no statistical significant difference in mortality between users of ACEi/ARBS and non-users (López-Otero (8 out of 78 ACEi/ARBS users died): OR, 0.62; 95%CI, 0.17-2.26; $P=0.486$, Imam: adjusted OR 1.20; 95%CI 0.86-1.68; $P=0.278$). López-Otero found that the absence of an impact on mortality remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year.

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -0.1 (95%CI -3.7 to 3.5) meaning that there was no statistically significant difference between both groups.

None of the studies showed a statistically significant difference between ACEi or ARBS use and non-users with regard to mortality (or a composite outcome including mortality).

1.1.2 ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -1.4 (95%CI -6.1 to 3.3) meaning that there was no statistically significant difference between both groups.

Mancia (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.83 (95% CI 0.63–1.10).

Jung (2020) studied the relation between ACEi/ARBS use ($N=377$) and mortality. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. In a multivariate analysis (adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type) Jung found no statistical significant difference in mortality between users and non-users (adjusted OR, 0.88 ; 95% CI 0.53–1.44; $p=0.60$).

In the study of López-Otero (2020) 6 out of 50 ACEI users died. López-Otero found no statistically significant difference in a multivariate analysis (analysis adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 1.54; 95%CI 0.42-5.59).

Mehra (2020) (included in the review of Zhang) studied the relation between ARBS use and mortality and found an OR of 1.23 (95%CI 0.87-1.74).

None of the studies showed a statistically significant difference between ARBS use and non-users with regard to mortality (or a composite outcome including mortality).

1.1.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -1.9 (95%CI -6.6 to 2.8) meaning that there was no statistically significant difference between both groups.

Bean (2020) (included in the review of Mackay) found an adjusted OR for the composite outcome 'mortality and transfer to critical care within 7 days of symptom onset' of 0.29 (95%CI: 0.10-0.75) for ACEi use vs non-users. This paper was not peer-reviewed.

Mancia (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.91 (95% CI 0.69-1.21).

In the study of López-Otero (2020) 2 out of 29 ACEI users died. López-Otero found no statistically significant difference in a multivariate analysis adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6 (OR 0.14; 95% CI 0.01-1.57).

Mehra (2020) (included in the review of Zhang) studied the relation between ACEI use and mortality and found an OR of 0.33 (95% CI 0.20-0.54).

Three studies showed no statistically significant difference between ACEI use and non-users with regard to mortality (or a composite outcome including mortality). Two studies (one not peer reviewed and assessed mortality within 7 days of symptom onset) showed a statically significant difference.

1.1.4 NSAID

For NSAID use, Imam (2020) found that NSAID users had a statistical significant lower risk of mortality compared to non NSAID users in a multivariate analysis (adjusted for age, Initial Serum Creatinine, CCI, NSAID, HTN, ACE-I/ARB use, CKD) (OR 0.57; 95%CI 0.40-0.82; P=0.002).

1.1.5 Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -3.4 (95% CI -8.3 to 1.6).

1.2 Hypertensive patients

1.2.1 ACEI/ARBS

We were unable to provide a pooled estimate for mortality since some studies did not provide the absolute number of events or used a composite outcome measure. Therefore, the results of each of the studies were described separately.

Zhang (2020) performed a meta-analysis of seven studies in which hypertensive ACEI/ARB users were compared with hypertensive patients on other blood pressure lowering medication or no medication. In this meta-analysis Zhang observed no statistically significant difference in risk of mortality among those who used ACEI/ARB (OR 0.62; 95% CI 0.38-1.02; $P=0.059$, $I^2=74.8\%$) (figure 3.2).

Zhang (2020) found in meta-analysis of four studies that ACEI/ARB use in hypertensive patients was associated with a lower risk of mortality compared to those on non-ACEI/ARB antihypertensive drugs (OR 0.48, 95% CI 0.29-0.81; $P=0.006$; $I^2=0\%$).

Selçuk (2020) found that ACEI/ARBs use was associated with a higher risk of mortality (adjusted OR 3.66; 95%CI 1.11-18.18; $P=0.032$). The Kaplan-Meier curve analysis displayed that patients on ACE inh/ ARBs therapy had a higher incidence of in-hospital death than those who were not (log rank test p value $<.001$). Felice (2020) found no statistically significant association between ACEI/ARB use in hypertensive patients in a multivariate analysis (OR 0.56; 95% CI 0.17-1.83; $P=0.341$).

Gao (2020) found no statistically significant association between ACEI/ARB use in hypertensive patients in a multivariate analysis (adjusted OR 0.85; 95% CI 0.28-2.58; $P=0.774$).

Zhou (2020) found no statistically significant difference in mortality between ACEI/ARB use ($N=$ in hypertensive patients using Student's unpaired t-test. We calculated the OR which was 0.49 (95% CI 0.082-2.966).

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -0.5 (95%CI -4.3 to 3.2).

Most of the studies showed no statistically significant difference between ACEI/ARBS use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality). In the sub-analysis of Zhang (included only hypertensive patients on other than ACEI/ARBS drugs in the control group, so did not include hypertensive patients on no medication) and Selçuk a significant difference was found.

1.2.2 ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI -4.8 to 4.9).

Jung (2020) studied the relation between hypertensive ACEI/ARB users and hypertensive patients on other blood pressure lowering medication or no medication. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. Jung found that RAAS inhibitor use was not independently associated with a higher risk of mortality among hypertensive COVID-19 patients (adjusted OR 0.71; 95% CI 0.40-1.26; $P=0.25$) adjusted for age, sex, Charlson Comorbidity Index, immunosuppression, and hospital type.

Mehra (included in the review of Zhang) studied the relation between ARBS use and mortality. Mehra found an OR of 1.233 (95% CI 0.87-1.74).

None of the studies showed a statistically significant difference between ARBS use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality).

1.2.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -3.3 (-8.2 to 1.7).

Mehra (included in the review of Zhang) studied the relation between ACEI use and mortality. Mehra found an OR of 0.33 (95% CI 0.20-0.54).

The study showed no statistically significant difference between ACEI use in hypertensive patients and non-users with regard to mortality (or a composite outcome including mortality) and one study found a statistically significant difference.

1.2.4 Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI -4.5 to 5.7).

2. IC-admission

2.1 Overall

2.1.1 ACEI/ARBS

In the review of Mackay (2020) two studies assessed the relationship between ACEI/ARBs use and IC-admission (Rentsch and Reynolds). Rentsch (2020) found that admission to the IC was more likely to occur in patients using ACEI/ARBS compared to non-users (adjusted OR 1.69; 95% CI 1.01-2.84). This study was not peer-reviewed.

Reynolds (2020) studied the relation between ACEi or ARBS use and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -0.1 (95%CI -3.7 to 3.5) meaning that there was no statistically significant difference between both groups.

López-Otero (2020) found no statistically significant difference in a multivariate analysis (adjusted for arterial oxygen saturation $<95\%$, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.87; 95% CI 0.30-2.50; $P=0.798$).

Two studies showed no statistically significant difference and one study that was not peer reviewed showed a statistically significant difference.

2.1.2 ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -1.4 (95%CI -6.1 to 3.3) meaning that there was no statistically significant difference between both groups.

López-Otero (2020) found that 7 ARBS users were admitted to the intensive care unit. López-Otero (2020)

found no statistically significant difference in a multivariate analysis (adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.84; 95% CI 0.25-2.87 P=0.786).

2.1.3 ACEI

Bean (2020) (included in the review of Mackay) found an adjusted OR for the composite outcome 'mortality and transfer to critical care within 7 days of symptom onset' of 0.29 (95%CI: 0.10–0.75) for ACEi use vs non-users. This paper was not peer-reviewed.

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was –1.9 (95%CI –6.6 to 2.8) meaning that there was no statistically significant difference between both groups.

López-Otero (2020) found that 6 ACEI users were admitted to the intensive care unit. López-Otero (2020) found no statistically significant difference between ACEI users and non-users in a multivariate analysis (adjusted for arterial oxygen saturation <95%, diabetes mellitus, hypoxemia, hypercapnia, lymphocytes, creatinine, elevated troponin, ferritin, C-reactive protein, interleukin-6)(OR 0.97; 95% CI 0.22-4.16 P=0.962).

One study showed no statistically significant difference and one study that was not peer reviewed showed a statistically significant difference

Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was –3.4 (95% CI –8.3 to 1.6) meaning that there was no statistically significant difference between both groups.

2.2 Hypertensive patients

2.2.1 ACEI/ARBs

Felice (2020) found that admission to semi-intensive/intensive care units was less likely to occur in hypertensive patients using ARB or ACEI (adjusted OR 0.25 95% CI 0.09-0.66; P=0.006).

Selçuk (2020) found a statistically significant difference (P=0.001) between IC-admission for hypertensive ACEI/ARB users (50%) compared to hypertensive non-users (17.9%). No correction for confounders was applied.

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was –0.5 (95%CI –4.3 to 3.2).

One study found no statistically significant difference, one study found a statistically significant difference in favour of ARB/ACEI users and one study found a statistically significant difference in favour of non-users.

2.2.2 ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or

mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI -4.8 to 4.9), meaning there was no statistically significant difference.

2.2.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -3.3 (-8.2 to 1.7), meaning there was no statistically significant difference.

2.2.4 Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI -4.5 to 5.7), meaning there was no statistically significant difference

3. Hospital admission

3.1 Overall

3.1.1 ACEI/ARBS

López-Otero (2020) reported 731 patients admitted to the hospital (75.8%), of which 210 were ACEI/ARBS users. López-Otero concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation, <95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ACEI/ARBS users vs non-users (OR 0.85; 95% CI 0.45-1.64; P=0.638).

Rentsch (2020) (included in the review of Mackay) found in a multivariate analysis that there was no statistically significant difference between hospital admission in ACEI/ARBS users vs non-users (adjusted OR 1.24; 95% CI 0.79-1.95). This study was not peer-reviewed.

Two studies found no statistically significant difference (one of those studies was not peer-reviewed).

3.1.2 ARBS

López-Otero (2020) concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation <95%, age, sex, health personnel, institutionalized, dependency status, dementia, hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ARBS users (n=50) vs non-users (n=134) (OR 1.10; 95% CI 0.59-2.04 P=0.757).

3.1.3 ACEI

Rossi (2020) (included in the review of Mackay) performed a multivariate analysis and found an adjusted HR with ACEI (adjusted for age, sex, and Charlson comorbidity score) of 1.13 (95%CI 1.1-1.5). When the analysis was restricted to patients with cardiovascular disease the aHR was 1.12 (95%CI 0.82-1.54; (adjusted for age, sex, and Charlson comorbidity score).

López-Otero (2020) concluded in a multivariate analysis (adjusted for days with symptoms, fever, arterial oxygen saturation <95%, age, sex, health personnel, institutionalized, dependency status, dementia,

hypertension, dyslipidemia, ventricular dysfunction, lung disease, previous cancer, hypothyroidism, antiplatelet therapy) that there was no statistically significant difference in hospital admission in ACEI users (N=20) vs non-users (N=77) (OR 0.78; 95% CI 0.38-1.60 P=0.505).

3.2 Hypertensive patients

3.2.1 ACEI/ARBS

Felice (2020) concluded in a multivariate analysis (adjusted for gender, BMI, days with symptoms prior to admission, previous cardiovascular events, diabetes and cancer) that there was no statistically significant difference in hospital admission in hypertensive ACEI/ARBS users vs non-users OR 0.39 (95% CI 0.05-2.94; P=0.365).

4. Length of stay

4.2 Hypertensive patients

4.2.1 ACEI/ARBS

Selçuk (2020) assessed length of stay for hypertensive patients on ACEI/ARBS and hypertensive patients on other medication. There was no statistically significant difference between both groups ACE inh/ARBs users: 9 days $\pm$ 6, Non-user 8 days $\pm$ 4 (P=0.524).

Zhou (2020) found no statistically significant difference (P=0.405) in hospital length of stay in hypertensive patients using ACEI/ARB (mean 10.1 days, SD 5.2) and hypertensive patients using other antihypertensive drugs (mean 11.7, SD 6.0). We calculated the mean difference between the groups which was 1.60 (95% CI- 2.31-5.51).

Two studies found no statistically significant difference.

5. Ventilation

Ventilation was defined differently in each of the studies. Jung assesses mechanical ventilation, Felice assesses oxygen therapy and non-invasive ventilation, Gao assesses invasive mechanical ventilation, Mancina assisted ventilation and Selçuk endotracheal intubation.

5.1 Overall

5.1.1 ACE/ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -0.1 (95%CI -3.7 to 3.5) meaning that there was no statistically significant difference between both groups.

5.1.2 ARBs

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -1.9 (95%CI -6.6 to 2.8) meaning that there was no statistically significant difference between both groups.

Jung (2020) studied the relation between ACEI/ARBS use and ventilation (mechanical ventilation). Since most of the included patients only used ARBS the results of this paper were used for the ARBS only category. Jung calculated an adjusted OR of 1.03 (95% CI 0.50-2.13; P=0.93).

Mancia (2020) (included in the review of Mackay) studied the relation between ARBS and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.83 (95% CI 0.63–1.10).

Three studies found no statistically significant difference.

5.1.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -1.9 (95%CI -6.6 to 2.8) meaning that there was no statistically significant difference between both groups.

Mancia (2020) (included in the review of Mackay) studied the relation between ACEI and the composite outcome 'severe COVID-19' defined as assisted ventilation or death. The adjusted OR was 0.91 (95% CI 0.69–1.21).

Two studies found no statistically significant difference.

5.1.4 Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -3.4 (95% CI -8.3 to 1.6) meaning that there was no statistically significant difference between both groups.

5.2 Hypertensive patients

5.2.1 ACEI/ARBS

Gao (2020) compared users of RAAS inhibitors (5;2.7%) with non-RAAS inhibitor users (25;4.7%) and found no statistically significant difference ($P=0.292$). Felice (2020) found an adjusted OR 0.58; 95%CI 0.21-1.60; $P=0.296$. Selçuk (2020) reported a statistically significant difference between ACEI/ARBS users (44.6% required ventilation) vs non-users (10.3% require ventilation) ($P<0.001$), however there was no correction for confounders performed.

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEi or ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -0.5 (95%CI -4.3 to 3.2).

5.2.2 ARBS

Reynolds (2020) (included in the review of Mackay) studied the relation between ARBS use in hypertensive patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.1 (95% CI -4.8 to 4.9) meaning that there was no statistically significant difference between both groups.

5.2.3 ACEI

Reynolds (2020) (included in the review of Mackay) studied the relation between ACEI use in hypertensive

patients and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was -3.3 (-8.2 to 1.7) meaning that there was no statistically significant difference between both groups.

5.2.4 Thiazolidinediones

Reynolds (2020) studied the relation between thiazide diuretics and the composite outcome 'severe COVID-19', defined as ICU admission, use of noninvasive or mechanical ventilation, or death. The mean difference between users and non-users of this medication was 0.6 (95% CI -4.5 to 5.7) meaning that there was no statistically significant difference between both groups.

6. Thromboembolic complications

6.1 Overall

6.1.1 ACEI/ARBS

López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ACEI/ARBS users and non-users (OR 1.37 ; 95% CI 0.39 - 4.77 ; $P=0.622$). The absence of an impact on heart failure remained both in the multivariate analysis and in the propensity score model, including in the evaluation of treatment taken for more than 1 year.

6.1.2 ARBS

Jung (2020) reported on acute cardiac event defined as cardiac arrest, myocardial infarction or acute heart failure. Since most of the included patients only used ARBS the results of this paper are used for the ARBS only category. No statistically significant differences were observed between RAAS inhibitor users and nonusers in terms of acute cardiac injury (OR 0.88 ; 95% CI 0.59 1.31 ; $P=0.53$).

López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ARBS users and non-users (OR 0.46 ; 95% CI 0.12 - 1.72 $P=0.248$).

6.1.3 ACEI

López-Otero (2020) reported on heart failure (defined according to the European Society of Cardiology guidelines). In a multivariate analysis, there was no statistically significant difference between ACEI users and non-users (OR 3.01 95%CI 0.89 - 10.16 $P=0.076$).

Level of Evidence

The level of evidence was assessed according to the GRADE methodology (GRADE: Grading Recommendations Assessment, Development and Evaluation, <http://www.gradeworkinggroup.org/>).

1. Mortality

1.1 Overall

ACEI/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (not all studies corrected for confounders, number of events sometimes not reported) to 'moderate'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (not all patients may have reached the outcome mortality yet and were still hospitalized at the moment of analysis) and one level for indirectness (two studies used a composite outcome measure) to 'low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (one study not peer reviewed, not all patients may have reached the outcome mortality yet and were still hospitalized at the moment of analysis), one level because of indirectness (two studies used a composite outcome measure and one study assessed 7-day mortality) to 'low'.

NSAID

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (unable to assess if the groups are comparable and information is unavailable on how many patients were still hospitalized at the moment of analysis) and two levels for imprecision (only one study available, small number of patients included) to 'very low'.

Thiazolidinediones

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level for indirectness (a composite outcome measure was used) to 'low'.

1.2 Hypertensive patients

ACE/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (number of events sometimes not reported but only ORs), and one level for imprecision (difference in effect size) to 'low'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), and one level because of indirectness (one study used a composite outcome measure) to 'low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (some

studies show a statistically significant difference and some do not) and one level because of indirectness (a composite outcome measure was used) to 'very low'.

Thiazolidinediones

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure mortality was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

2. IC admission

2.1 Overall

ACE/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (one study not peer reviewed, follow up duration unclear), one level because of imprecision (some studies show no effect, one study shows a significant effect) and one level because of indirectness (in one study a composite outcome measure was used) to 'very low'.

ARBS

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could be admitted to the IC at a later moment), one level for indirectness (one study used a composite outcome measure) and one level for imprecision (small number of events) to 'very low'.

ACE

Starting with a high of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could be admitted to the IC at a later moment), one level for indirectness (one study used a composite outcome measure) and one level because of imprecision (low number of events) to 'very low'.

Thiazolidinedione

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

2.2 Hypertensive patients

ACEI/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias and one level for imprecision (wide range of effects) and one level because of indirectness (a composite outcome

measure was used in one study and in one study the outcome was semi intensive care or intensive care) to 'very low'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

Thiazolidinedione

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure IC admission was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

3. Hospital admission

3.1 Overall

ACE/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by two levels because of risk of bias (one study not peer reviewed, follow up duration unclear) to 'low'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (follow up duration unclear), one level for imprecision (small number of events) to 'low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (follow up duration unclear), one level for imprecision (small number of events, one study shows a statistically significant, the other does not) to 'low'.

3.2 Hypertensive patients

ACE/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure hospital admission was downgraded by one level because of risk of bias (the

study only included hypertensive subjects who presented to the emergency department with acute respiratory symptoms/fever), and two levels because of imprecision (small sample size, wide CI) to 'very low'.

4. Length of stay

4.2 Hypertensive patients

ACEI/ARBs

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure length of stay was downgraded by two level because of risk of bias (no correction for confounders, in one study follow up duration unclear) and one level because of imprecision (small number of included patients) to 'very low'.

5. Ventilation

5.1 Overall

ACE/ARBs

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

ARBs

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (wide confidence interval) and one level because of indirectness (a composite outcome measure was used in two studies) to 'very low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis), one level for imprecision (wide confidence interval) and one level because of indirectness (a composite outcome measure was used in two studies) to 'very low'.

Thiazolidinediones

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

5.2 Hypertensive patients

ACEI/ARBs

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some studies did not correct for confounding), one level for imprecision (some studies describe a significant difference, some studies found no significant difference) and one level because of indirectness (composite outcome measure, different definitions of ventilation) to 'very low'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

Thiazolidinediones

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure ventilation was downgraded by one level because of risk of bias (some patients may not have reached the outcome yet by the date of analysis) and one level because of indirectness (a composite outcome measure was used) to 'low'.

6. Tromboembolic complications

6.1 Overall

ACEI/ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as heart failure) and one level because of imprecision (small number of events) to 'very low'.

ARBS

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as heart failure in one study and in one study a small number of patients in the I group were using ACEI) and one level because of imprecision (small number of events) to 'very low'.

ACEI

Starting with a high level of evidence for observational studies (prognostic question), the level of evidence

regarding the outcome measure thromboembolic complications was downgraded by 1 level because of risk of bias (some patients were still hospitalized at the moment of analysis and still could develop thromboembolic complications), one level because of indirectness (thromboembolic complications was defined as heart failure) and one level because of imprecision (wide confidence interval) to 'very low'.

Zoeken en selecteren

A review of the literature was performed to answer the following question:

What is the effect of using medication that influence ACE-2 expression (ACEi, ARBs, NSAIDs and thiazolidinediones) on the outcomes in patients with COVID-19?

P: All proven COVID-19 patients

I: Using medication before and during COVID-19 that influence ACE-2 expression: ACEi, ARBs, NSAIDs and thiazolidinediones

C: No use of medication that influence ACE-2 expression before and during COVID-19

O: Mortality, IC-admission, hospital admission, length of stay, thromboembolic complications (pulmonary embolism, stroke, transient ischemic attack), ventilation.

Relevant outcome measures

Mortality was considered as critical outcome measure for decision making and the other outcomes as important outcomes for decision making.

A priori, the working group did not define minimal clinically relevant differences for the outcome measures.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until June 24th, 2020. The systematic literature search resulted in 567 hits. See search strategy for detail. 64 studies were initially selected based on title and abstract screening. After reading the full text, 56 studies were excluded (see the table with reasons for exclusion under the tab Methods), and nine studies were included.

Results

Nine studies were included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias table.

Verantwoording

Laatst beoordeeld :

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Startpagina - Langdurige klachten en revalidatie na COVID-19

Waar gaan deze richtlijnmodules over?

Deze richtlijnmodules geven adviezen over de zorg voor patiënten die COVID-19 hebben doorgemaakt. De modules zijn onderverdeeld in 4 overkoepelende onderwerpen:

- indicatie voor/inhoud van de medisch-specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ) na een opname in het ziekenhuis of eerstelijnsverblijf hoog complex
- voorlichting over het beloop, adviezen en diagnostiek in de eerste lijn (in herziening)
- follow-up, diagnostiek en multidisciplinair overleg in de tweede lijn (in herziening)
- behandeling van langdurige klachten (in herziening)

Voor patiënten

Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over [COVID-19](#). Daarnaast is aanvullende informatie beschikbaar op het [Coronaplein](#) en [C-support.nu](#).

Hoe zijn de richtlijnmodules tot stand gekomen?

De richtlijnmodules zijn ontwikkeld binnen de projecten:

- Richtlijn Revalidatie COVID-19
Dit project was een initiatief van de Nederlandse Vereniging van Revalidatieartsen en Verenso.
- Richtlijn Langdurige klachten na COVID-19
Dit project was een initiatief van het Nederlands Huisartsen Genootschap, de Federatie Medisch Specialisten en de Long Alliantie Nederland.

In de verantwoording van elke module staat gedetailleerd beschreven hoe het ontwikkelproces heeft plaatsgevonden en welke partijen bij de ontwikkeling betrokken waren.

Toepassing

De modules die zijn ontwikkeld binnen het project Richtlijn Langdurige klachten na COVID-19 zijn ook opgenomen op de NHG-richtlijnenwebsite. Binnen dit project is ook een [NHG-Standaard](#) ontwikkeld. Deze Standaard bestaat uit een tekst met aanbevelingen gericht op de huisartsenpraktijk, waarbij voor de onderbouwing wordt verwezen naar de richtlijnmodules die betrekking hebben op de eerste lijn. De aanbevelingen in de richtlijnmodules en in de Standaard komen inhoudelijk overeen. Bij deze richtlijnmodules zijn een e-learning module en een webinar ontwikkeld. Op 2 juni 2022 vond een webinar plaats, waarin drie thema's uit de richtlijn worden uitgelicht met specifieke ervaringen en uitdagingen uit de praktijk. [Kijk deze hier terug](#), gebruik het wachtwoord 0a5W%pyi. De e-learning was te volgen tot 2025.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Startpagina - Revalidatie na COVID-19

Waar gaan deze richtlijnmodules over?

Binnen deze modules worden aanbevelingen gedaan over

1. de indicatiestelling voor een revalidatietraject na ziekenhuisopname of opname in het eerstelijnsverblijf hoog complex (ELV-HC) voor COVID-19; en
2. de zorg binnen de (poli)klinische medisch specialistische revalidatie (MSR) of klinische of ambulante geriatrische revalidatiezorg (GRZ) aan volwassen patiënten met COVID-19 die recent zijn ontslagen uit het ziekenhuis of ELV-HC.

Specifiek komen de volgende onderwerpen aan de orde:

- indicatiestelling en herindicatie revalidatietraject;
- de meetinstrumenten;
- de waarde en invulling van de fysieke training;
- de waarde van adem oefeningen en ademspiertraining;
- de waarde van zuurstoftherapie en plaats van de saturatiemeter tijdens inspanning;
- de behandeling van mentale en cognitieve klachten;
- de behandeling van slikklachten; en
- de waarde van specifieke voedingsinterventies.
- overleg- en doorverwijsmogelijkheden;

Voor wie zijn deze richtlijnmodules bedoeld?

Deze richtlijn is ontwikkeld voor alle leden van de beroepsgroepen die betrokken zijn bij de indicatiestelling voor het revalidatietraject bij patiënten opgenomen met COVID-19 in het ziekenhuis of eerstelijnsverblijf (hoog complex), alsmede alle leden van de beroepsgroepen die betrokken zijn bij de zorg aan patiënten binnen de MSR en GRZ.

Informatie voor patiënten en naasten

Bij patiënten die in het ziekenhuis of een zorginstelling hebben gelegen met corona omdat zij erg ziek waren, kijkt de arts samen met de patiënt waar deze het beste kan herstellen. Hierbij zijn verschillende opties: veel patiënten kunnen terug naar huis met zorg van de huisarts, met eventueel thuiszorg en/of begeleiding van therapeuten. Indien er nog veel klachten of beperkingen zijn, kan uitgebreidere revalidatie nodig zijn. Dit kan in een revalidatiecentrum of in een zorginstelling voor (geriatrische) revalidatie, maar ook thuis of vanuit thuis waarbij er begeleiding vanuit een (geriatrisch) revalidatiecentrum wordt gegeven.

Deze richtlijn gaat over de keuze waar en hoe patiënten na een ziekenhuisopname of opname in een zorginstelling het beste kunnen revalideren. Daarnaast wordt in deze richtlijn de behandeling in een revalidatiecentrum of zorginstelling voor (geriatrische) revalidatie beschreven. Hierbij kan gedacht worden aan welke testen en vragenlijsten afgenomen kunnen worden, maar ook over de inhoud van de behandeling en de organisatie van zorg.

Zie ook de informatie op [Thuisarts.nl](https://thuisarts.nl):

Voor patiënten die in het ziekenhuis hebben gelegen:

[Ik heb in het ziekenhuis gelegen met corona](#)

Voor patiënten die op de IC hebben gelegen:

[Ik heb op de IC gelegen met corona](#)

Voor patiënten die in het ziekenhuis hebben gelegen en naar een verpleeghuis of revalidatiecentrum gaan:

[Ik heb in het ziekenhuis gelegen met corona en ga naar een verpleeghuis of revalidatie-centrum](#)

Voor de naasten van een patiënt die in het ziekenhuis hebben gelegen en naar een verpleeghuis of revalidatiecentrum gaat:

[Mijn naaste heeft in het ziekenhuis gelegen met corona en gaat naar een verpleeghuis of revalidatie-centrum](#)

Hoe zijn deze richtlijnmodules tot stand gekomen?

Deze modules zijn in 2021 ontwikkeld op initiatief van de Nederlandse Vereniging van Revalidatieartsen (VRA) en Verenso. De richtlijn is opgesteld door een multidisciplinaire commissie met vertegenwoordigers vanuit de revalidatieartsen, specialisten ouderengeneeskunde, diëtisten, ergotherapeuten, fysiotherapeuten, klinisch geriaters, logopedisten, longartsen, psychologen, sportartsen, verpleegkundigen en afvaardiging vanuit het Longfonds. Afgevaardigden vanuit Revalidatie Nederland en de Vereniging van Oefentherapeuten Cesar en Mensendieck hebben met de richtlijn meegelezen.

Bij meerdere modules is gebruik gemaakt van reeds ontwikkelde documenten, zoals de 'Leidraad Nazorg voor patiënten met COVID-19' (Federatie Medisch Specialisten, 2020) en het 'Behandeladvies Post-COVID-19 (geriatrische) revalidatie' (Verenso, 2020). Dit wordt in de betreffende modules nader toegelicht.

Toepassen

Bij de module '[Indicatiestelling revalidatietraject](#)' is een [stroomschema](#) gemaakt.

Verantwoording

Laatst beoordeeld : 24-09-2021

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Indicatiestelling revalidatietraject en hertriage bij COVID-19

Uitgangsvraag

Bij welke patiënten met COVID-19 opgenomen in het ziekenhuis of in het eerstelijnsverblijf (hoog complex) moet een revalidatietraject in de post-acute fase overwogen worden? En indien een revalidatietraject geïndiceerd is, welke is dan passend?

Aanbeveling

Tijdens ziekenhuisopname/opname in het eerstelijnsverblijf (hoog complex) voor COVID-19

Bepaal bij elke patiënt zo vroeg mogelijk tijdens opname of er een indicatie voor een revalidatietraject is (zie ook het stroomschema (Figuur 1) en Tabel 1). Overweeg hiervoor een MDO en/of consultatie revalidatiearts en/of specialist ouderengeneeskunde.

Tijdens de behandeling binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg

Evalueer regelmatig met de patiënt en in multidisciplinair overleg of het gekozen traject passend is, en her-trieer waar nodig bij toegenomen of afgenomen belastbaarheid, verandering van revalidatiedoelen of bij andere belangrijke wijzigingen.

Overwegingen

Stellen van de indicatie en maken van een keuze voor het nazorgtraject na ziekenhuisopname of een opname in het eerstelijnsverblijf hoog complex (ELV-HC)

Of de patiënt in aanmerking komt voor een revalidatietraject en welk traject het meest passend is hangt af van de hulpvraag en motivatie van de patiënt, patiënt karakteristieken, zoals kwetsbaarheid, belastbaarheid, complexiteit van de zorgvraag (noodzaak tot frequente medische nazorg en verpleegkundige handelingen), premorbide functioneren, en welke doelen behaald dienen te worden (Triage Instrument Geriatrische Revalidatiezorg, Verenso, 2013; Indicatiestelling Medisch Specialistische Revalidatie, VRA en RN, 2016). Daarnaast spelen in de te maken keuzes de beschikbaarheid en capaciteit van faciliteiten, lokale voorzieningen en beschikbaarheid van personeel gedurende de besmettingsgolven een rol. Aanbevolen wordt om de indicatiestelling voor het revalidatietraject op een zo vroeg mogelijk moment in het ziektebeloop te stellen, bij voorkeur in een multidisciplinair overleg (MDO). In dit MDO dient een zorgvuldige inventarisatie van de zorg-, behandel- en revalidatiebehoefte te worden verricht. De afweging voor revalidatie en de planning van het nazorgtraject kan in overleg met het behandelteam inclusief verwijzend specialist worden verricht. In principe wordt de indicatie voor revalidatie door de revalidatiearts en/of specialist ouderengeneeskunde (of, in kader van taakherschikking door een ter zake bekwame verpleegkundig specialist of physician assistant) vastgesteld (Federatie Medisch Specialisten, 2020; Triage Instrument Geriatrische Revalidatiezorg, Verenso, 2013, Handreiking Taakherschikking, Verenso, 2012-2017). Dit kan door het in kaart brengen van het premorbide niveau van functioneren, premorbide comorbiditeiten, sociale omstandigheden, fysiek, psychisch en cognitief functioneren. In combinatie met het huidig functioneren, bijkomende intercurrent opgetreden aandoeningen en beloop van herstel en inschatting van belastbaarheid gedurende de ziekenhuisopname, geeft dit aanwijzingen over de te verwachten medische complicaties en de prognose

ten aanzien van terugkeer naar huis en welk revalidatietraject het meest passend is (zie ook Tabel 1, Figuur 1 en de onderstaande toelichting op de mogelijke trajecten). Vanzelfsprekend wordt deze keuze samen met de patiënt (en naaste) gemaakt.

Het eerder beschreven MDO bevordert snelle uitplaatsing naar passende (ambulante) nazorg en draagt bij aan de continuïteit van behandeling voor de patiënt. Voor overplaatsing dienen een aantal randvoorwaarden, waaronder zuurstofbehoefte, kort te worden gesloten. Ook bij vervoegd ontslag van een COVID-19 patiënt met zuurstofbehoefte naar een andere zorglocatie of thuis, dient nagegaan te worden of patiënt in aanmerking komt voor geriatrische dan wel medisch specialistische revalidatiezorg.

Hieronder, in Tabel 1 en Figuur 1 zetten wij kort uiteen welke nazorgtrajecten de patiënten na ontslag uit het ziekenhuis kunnen volgen.

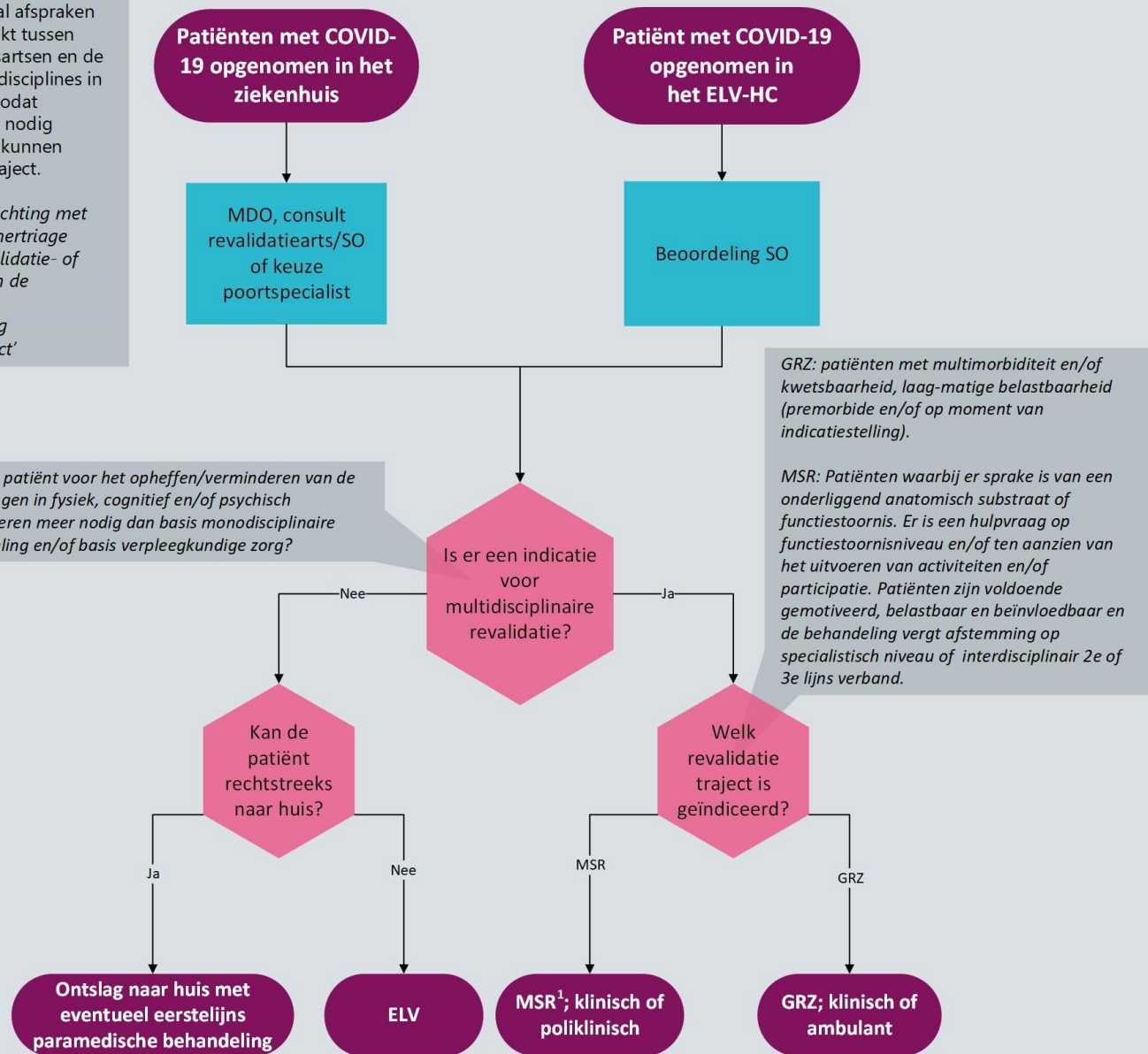
Tabel 1 Overzicht mogelijke nazorgtrajecten patiënten met COVID-19

Patiëntengroep	Nazorgtraject
Patiënten met milde klachten en/of beperkingen.	Ontslag naar huis met indien geïndiceerd verwijzing naar eerstelijns paramedische behandeling.
Patiënten die (nog) geen indicatie voor interdisciplinaire revalidatie hebben, maar die nog hulp nodig hebben bij herstel en verzorging en niet rechtstreeks naar huis kunnen. Vaak bekend met co-morbiditeit, premorbide kwetsbaar en laag-matig belastbaar.	Eerstelijnsverblijf (ELV)
Patiënten met multimorbiditeit en/of kwetsbaarheid, laag-matige belastbaarheid (premorbiditeit en/of op moment van indicatiestelling), waarbij er sprake is van beperkingen in fysiek, cognitief en/of psychisch functioneren waarvoor interdisciplinaire revalidatie nodig is met ouderengeneeskundige expertise.	Geriatrische revalidatiezorg (GRZ; klinisch of ambulant)
Patiënten met beperkingen in het fysiek, cognitief en/of psychisch functioneren, waarbij er sprake is van een onderliggend anatomisch substraat of functiestoornis. Er is een hulpvraag op functiestoornisniveau en/of ten aanzien van het uitvoeren van activiteiten en/of participatie. Patiënten zijn voldoende gemotiveerd, belastbaar en beïnvloedbaar en de behandeling vergt afstemming op specialistisch niveau of interdisciplinair 2e of 3e lijns verband. Indien bij deze patiënten longklachten op de voorgrond staan is revalidatie bij een centrum voor CCL eerste keus.	Medisch specialistische revalidatie (MSR; klinisch of poliklinisch) Kenniscentra Complex Chronische Longaandoeningen (CCL; klinisch of poliklinisch)

Figuur 1 Mogelijke nazorgtrajecten patiënten met COVID-19
NB:

Het is van belang dat er lokaal/regionaal afspraken worden gemaakt tussen GRZ, MSR, huisartsen en de paramedische disciplines in de eerste lijn, zodat patiënten waar nodig laagdrempelig kunnen wisselen van traject.

Zie ook de toelichting met betrekking tot hertriage tijdens het revalidatie- of nazorgtraject in de richtlijnmodule 'Indicatiestelling revalidatietraject'


Voetnoot:

1. Indien bij deze patiënten longklachten op de voorgrond staan, is revalidatie in één van de vijf kenniscentra Complex Chronische Longaandoeningen eerste keus.

Afkortingen:

ELC-HC: eerstelijnsverblijf hoog complex
GRZ: geriatrie revalidatiezorg
MDO: multidisciplinair overleg

MSR: medisch specialistische revalidatie
SO: specialist ouderengeneeskunde

Hieronder volgt een korte toelichting op de mogelijke trajecten

Ontslag naar huis

Patiënten met milde klachten en/of beperkingen waarbij er geen vervolgtraject binnen de (MSR) of (GRZ) is geïndiceerd, zullen naar huis worden ontslagen. Bepaal in overleg of de zorg gecoördineerd wordt door de huisarts of de poortspecialist[1]. De huisarts kan gebruik maken van de adviezen beschreven in de module 'Patiënten behandeld in eerste lijn' van de leidraad 'Nazorg voor patiënten met COVID-19', (Federatie Medisch Specialisten, 2020; deze leidraad wordt waarschijnlijk in 2022 vervangen door de integrale richtlijn 'Nazorg voor patiënten met COVID-19'), eventueel in samenwerking met bijvoorbeeld eerstelijns paramedici en een psycholoog. Op dit moment (voorjaar 2021) is het voor de bekostiging door de zorgverzekering belangrijk dat de verwijzing naar de paramedici binnen zes maanden na acute fase plaats vindt.

Eerstelijnsverblijf hoog complex (ELV-HC)

Het ELV-HC is bedoeld voor patiënt waarbij de gezondheidssituatie tijdelijk verandert of dreigt te veranderen, waardoor de medische (en verpleegkundige) zorg thuis ontoereikend is en de huisarts een opname in een ziekenhuis niet nodig of wenselijk acht. Het ELV-HC omvat medisch noodzakelijke zorg zoals een specialist ouderengeneeskunde en diens team die bieden (Afwegingsinstrument, 2016). Het ELV-HC biedt geen ruimte voor interdisciplinaire revalidatie, de mogelijkheden voor paramedische therapie zijn te beperkt.

Geriatrische revalidatiezorg (GRZ)

GRZ is vooral bedoeld voor ouderen (leeftijd is echter geen absoluut criterium) met beperkte belastbaarheid en vaak bijkomende multimorbiditeit en/of kwetsbaarheid, waarbij er sprake is van beperkingen in fysiek, cognitief en/of psychisch functioneren waarvoor interdisciplinaire revalidatie nodig is. Deze patiënten zijn meestal (deels) zorgafhankelijk bij de start van de revalidatie en (zeer) beperkt belastbaar. Doelen zijn grotendeels functioneel en op ADL (algemene dagelijkse levensverrichting) zelfstandigheid gericht, maar ook (beperkte) participatiedoelen zijn mogelijk. Ook bij zeer kwetsbare patiënten met te verwachten medische complicaties en onduidelijke prognose ten aanzien van terugkeer naar huis, kan GRZ geïndiceerd zijn wanneer er tevens (bescheiden) revalidatie doelen aanwezig zijn. Patiënten dienen wel voldoende leerbaar te zijn om functioneel te kunnen trainen.

Indicatiestelling voor GRZ verloopt via een specialist ouderengeneeskunde (of waargenomen door een ter zake bekwame verpleegkundig specialist of physician assistant vanuit het geriatrische revalidatiecentrum), en wordt bij voorkeur in een MDO-setting besproken, zie ook Triage Instrument Geriatrische Revalidatiezorg.

Medische specialistische revalidatiezorg (MSR)

MSR is vooral bedoeld voor patiënten met beperkingen in het fysiek, cognitief en/of psychisch functioneren, waarbij er sprake is van een onderliggend anatomisch substraat of functiestoornis. Er is een hulpvraag op functiestoornisniveau en/of ten aanzien van het uitvoeren van activiteiten en/of participatie. Patiënten zijn voldoende gemotiveerd, belastbaar en beïnvloedbaar en de behandeling vergt afstemming op specialistisch niveau of interdisciplinair 2e of 3e lijns verband. Voor MSR direct na ontslag uit het ziekenhuis verloopt de aanmelding via de consulent revalidatiearts (of een ter zake bekwame verpleegkundig specialist of physician assistant) van het ziekenhuis. Voor de indicatiestelling zijn afspraken gemaakt met diverse partijen, zie ook de nota Indicatiestelling Medisch Specialistische Revalidatie. Patiënten kunnen binnen de MSR zowel klinisch als poliklinisch worden behandeld.

Kenniscentra Complex Chronische Longaandoeningen (CCL)

Voor patiënten waarbij complexe longklachten op de voorgrond staan kan de revalidatie in overleg met de longarts ook plaatsvinden in een gespecialiseerd longcentrum. Meer informatie over deze centra is beschikbaar op en via de website van de Kenniscentra Complex Chronische Longaandoeningen (<https://kenniscentraccl.nl>).

Overwegingen hertriage tijdens het revalidatie- of nazorgtraject

Soms is het lastig om goed in te schatten waar de patiënt het beste behandeld kan worden. Ook kan het verloop van het herstel (bijvoorbeeld met betrekking tot de belastbaarheid of sneller herstel dan verwacht) aanleiding geven tot verandering van het traject. Het is daarom van belang dat er lokaal of regionaal afspraken worden gemaakt tussen de geriatrische revalidatiezorg (GRZ), medisch specialistische revalidatie (MSR), de huisartsen en de paramedische disciplines in de eerste lijn, zodat patiënten laagdrempelig kunnen wisselen naar een meer passend traject. Hertriage in het beloop van de revalidatie wordt geadviseerd bij veranderingen in belastbaarheid, verandering van revalidatiedoelen of bij andere belangrijke wijzigingen. Uiteraard moet er aandacht zijn voor de individuele wensen van de voor revalidatie geïndiceerde patiënt, die goed besproken moeten worden en als uitgangspunt dienen voor elke nieuwe interventie.

De werkgroep realiseert zich dat hertriage vanuit het oogpunt van financiering niet altijd haalbaar is. In sommige regio's zijn er financiële problemen/uitdagingen (niet alle zorgverzekeraars handelen hier eenduidig op). Regionale samenwerking tussen de diverse actoren betrokken bij de behandeling en revalidatie van COVID-19, zowel in als buiten de ziekenhuiszorg, is van groot belang om een optimale zorg te kunnen bieden, rekening houdend met lokale voorzieningen. De mogelijkheid bestaat zo om indien noodzakelijk te veranderen van gekozen behandelmodaliteit.

[1] Een poortspecialist is de medisch specialist naar wie een patiënt wordt verwezen voor medisch specialistische zorg.²²

Onderbouwing

Achtergrond

Infectie met SARS-CoV-2 presenteert zich met (zeer) milde tot zeer ernstige klachten die zich kunnen uiten in verschillende domeinen; zowel fysiek, sociaal-maatschappelijk, cognitief en/of psychisch. Het beloop van de ziekte maakt dat er goede voorzieningen nodig zijn voor het hersteltraject. Afhankelijk van onder andere restklachten en premorbide niveau van functioneren zijn er verschillende nazorgtrajecten na opname in ziekenhuis of eerstelijnsverblijf mogelijk: Medisch specialistische revalidatie (MSR), revalidatie in één van de Kenniscentra Complex Chronische Longaandoeningen (KCCL), geriatrische revalidatiezorg (GRZ), revalidatie in Wet Langdurige Zorg (WLZ zorgzwaartepakket 9B), eerstelijnsverblijf (ELV) hoog-complex (HC), ELV laag-complex en ELV palliatief, thuiszorg/wijkverpleging en (mono- of multidisciplinaire) behandeling door eerstelijns zorgprofessionals.

Indien patiënten die in het ziekenhuis opgenomen zijn geweest of de acute fase hebben doorgemaakt in een ELV-HC (omdat thuis onvoldoende zorg geboden kon worden) een klinisch revalidatietraject behoeven kan

dit plaats vinden binnen de medisch specialistisch revalidatie (MSR), geriatrische revalidatiezorg (GRZ) of bij één van de KCCL. Indien de patiënt in staat is om naar huis terug te keren, maar wel revalidatiedoelen heeft, kan dit in de MSR, GRZ of KCCL (poliklinisch of ambulant) plaats vinden of door middel van eerstelijns paramedische behandeling. In deze module worden aanbevelingen gedaan met betrekking tot de indicatiestelling voor een revalidatietraject bij patiënten die met COVID-19 zijn opgenomen in ziekenhuis of ELV-HC. Ook is er aandacht voor hertriage tijdens het revalidatietraject.

Zoeken en selecteren

Er is geen search uitgevoerd, omdat het niet de verwachting was dat er onderzoek beschikbaar is die deze uitgangsvraag beantwoord. Als deze onderzoeken er wel zouden zijn, dan is echter de kans ook groot dat de resultaten van dit onderzoek niet van toepassing zijn op de Nederlandse situatie. De uitgangsvraag is daarom beantwoord met behulp van 1) de leidraad 'Nazorg voor patiënten met COVID-19' (Federatie Medisch Specialisten, 2020) en het 'Behandeladvies Post-COVID-19 (Geriatrische) revalidatie' (Verenso, 2020); 2) de expertise van de werkgroep die uit verschillende disciplines bestaat; en 3) bestaande afspraken met betrekking tot de indicatiestelling.

Verantwoording

Laatst beoordeeld : 24-09-2021

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Fysieke training binnen de MSR/GRZ na COVID-19

Uitgangsvraag

Wat is de waarde van een gestructureerd fysiek trainingsprogramma bij patiënten die opgenomen zijn geweest in het ziekenhuis of eerstelijnsverblijf met COVID-19 en behandeld worden binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg? En indien deze interventie van meerwaarde is, hoe zou deze er dan uit moeten zien?

Aanbeveling

Bied patiënten binnen de MSR of GRZ die COVID-19 hebben doorgemaakt gesuperviseerde fysieke training aan, tenzij er sprake is van een absolute contra-indicatie (Tabel 1). Bij een relatieve contra-indicatie (Tabel 1), overleg eerst met de behandelend arts, of een terzake bekwaam verpleegkundig specialist of physician assistant.

Bepaal samen met de patiënt het huidige en het gewenste niveau van functioneren vast. Stel op basis hiervan een trainingsprogramma op.*

Monitor de belastbaarheid van de patiënt gedurende de training en gedurende de trainingsperiode. Pas waar nodig de trainingsintensiteit aan en/of geef adviezen over de energieverdeling over de dag.

Motiveer de patiënt om ook na afloop van het revalidatietraject een actieve en gezonde levensstijl aan te houden.

** Voor aanbevelingen met betrekking tot zuurstofsuppletie tijdens inspanning wordt verwezen naar de module Zuurstoftherapie (in ontwikkeling)*

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek uitgevoerd naar de effecten van een gestructureerd trainingsprogramma bij patiënten die COVID-19 hebben doorgemaakt. Er is slechts één prospectieve cohort studie geïnccludeerd in de literatuursamenvatting.

De studie includeerde patiënten (n=106) die ontslagen waren uit het ziekenhuis na opname wegens COVID-19. Het is onduidelijk in hoeverre de resultaten zijn te generaliseren naar de setting van de medisch specialistische revalidatie (MSR) of de geriatrische revalidatiezorg (GRZ). De studie was verder een observationele studie, zonder randomisatie van patiënten en blinding van patiënten en beoordelaars. Daarnaast was er sprake van een relatief hoog aantal patiënten waarbij follow-up meting ontbrak. Dit resulteert in een hoog risico op vertekening van de studieresultaten (risk of bias) bij de geïnccludeerde uitkomstmaten.

De overall bewijskracht is zeer laag. De geïnccludeerde studie rapporteerde geen informatie over het fysiek functioneren (cruciale uitkomstmaat), kwaliteit van leven (cruciale uitkomstmaat), adverse events en

vermoeidheid, waardoor er geen uitspraak gedaan kan worden over het effect van een behandeling met en zonder een gestructureerd trainingsprogramma omtrent deze uitkomstmaten. Op basis van de gevonden resultaten is het daarnaast onduidelijk of fysieke fitheid en spierkracht verschillen na behandeling met en zonder een gestructureerd trainingsprogramma.

Hoewel er op dit moment dus nog weinig wetenschappelijke onderbouwing is bij patiënten die COVID-19 hebben doorgemaakt, is de werkgroep van mening dat gesuperviseerde fysieke training een belangrijk onderdeel is van de medisch specialistische revalidatie (MSR) of geriatrisch revalidatiezorg (GRZ). De werkgroep raadt daarom fysieke training binnen de MSR en GRZ aan, analoog aan richtlijnen bij andere patiëntpopulaties (ook buiten de MSR en GRZ) waarbij de fysieke fitheid daalt door de aandoening of behandeling (ADA, 2019; Piepoli, 2011, Thompson, 2003; Aboyans, 2018; Williams, 2018; Garvey, 2016; Ries, 2007; Campbell, 2019).

Er zijn drie argumenten die het aannemelijk maken dat de fysieke fitheid is afgenomen bij COVID-19 patiënten die behandeld worden binnen de MSR en GRZ:

- Immobilisatie/ inactiviteit

Bij veel patiënten zal er sprake zijn van deconditionering door langdurige immobilisatie/ inactiviteit op de IC of op de ziekenhuisafdeling. Bedrust veroorzaakt bij gezonde proefpersonen een sterke daling van de maximale zuurstofopname ($VO_2\text{max}$; 0,43% per dag)⁹. Na 20 dagen bedrust zonder aansluitend beweegprogramma kan er zelfs na 8-9 weken nog een 13% vermindering van $VO_2\text{max}$ bestaan (Kashihara, 1994).

- Infectie

Hoewel nog veel onduidelijk is in de pathofysiologie, is het aannemelijk dat de infectie zelf een negatief effect heeft op de fysieke fitheid (mogelijk vanwege pulmonale restpathologie, spierzwakte, moeheid) (Huang, 2021). Het is de verwachting dat met fysieke training deze deconditionering gedeeltelijk reversibel is, vergelijkbaar aan vele andere vormen van pathologie waarbij immobilisatie/inactiviteit of een ziekenhuisopname nodig is.

- Comorbiditeit

Ernstige COVID-19 treedt vaker op bij patiënten met comorbiditeit. Bijvoorbeeld patiënten met diabetes, obesitas en hypertensie hebben een hoger risico op een ernstiger beloop van COVID-19 (NG, 2021). Patiënten met deze aandoeningen hebben ook vaker een verminderde premorbide fitheid. In de bijlage van deze module zijn voorbeelden gegeven van medisch gerelateerde componenten die kunnen interacteren met de vaardigheden en gezondheid gerelateerde componenten/factoren.

Inhoud van het trainingsprogramma

Het is belangrijk dat de zorgverlener samen met de patiënt inventariseert wat het huidige en gewenste niveau van fysieke fitheid, functioneren en participatie is. Hier kan het trainingsprogramma op worden afgestemd.

Afhankelijk van de ernst van de infectie, de duur van immobilisatie, het wel of niet beademd zijn, het premorbide functioneren en de comorbiditeit zijn er binnen de patiëntenpopulatie grote verschillen in fysieke fitheid te verwachten. Om het huidige niveau van fysieke fitheid in kaart te brengen, kan een fysieke test afgenomen worden. De 'gouden standaard' voor het bepalen van de fysieke fitheid is een inspanningstest

met ademgasanalyse (CPET, VO₂ meting; ACSM 2009). Echter deze test is niet altijd voorhanden (gezien de beperkte beschikbaarheid expertise en apparatuur). Het afnemen van een CPET binnen de GRZ is zeer ongebruikelijk en binnen de MSR is er geen consensus over wanneer en bij wie de CPET ingezet moet worden. Er zijn, indien de CPET niet wordt ingezet, alternatieven (bijvoorbeeld de twee minuten looptest en de zes minuten looptest) beschikbaar. Een vragenlijst (zie de module Meetinstrumenten; in ontwikkeling) kan gebruikt kunnen worden om het gewenste niveau van functioneren in kaart te brengen.

De inhoud van een trainingsprogramma dient afgestemd te worden op de gevonden limitaties en de persoonlijke doelen van de patiënt. Gezien de schaarsheid aan wetenschappelijke literatuur, is het niet mogelijk om een specifiek programma of een specifieke dosering aan te raden. Binnen de MSR en GRZ is er echter veel ervaring met het trainen van patiënten, het is daarom de verwachting dat de meeste instellingen standaardprogramma's beschikbaar hebben die voldoen. Uit de enquête onder patiënten (zie de bijlage 'Resultaten enquête onder patiënten') blijkt dat de meeste patiënten tijdens de revalidatieperiode aan evenwichts- of stabiliteitsoefeningen, krachttraining en/of conditietraining hebben gedaan. Specifiek voor COVID-19 geldt wel dat een substantieel gedeelte van de patiënten aan de start van het revalidatietraject nog extra zuurstof krijgt. Voor de specifieke aspecten met betrekking tot de zuurstofsuppletie tijdens inspanning wordt verwezen naar de module Zuurstoftherapie (in ontwikkeling).

Mocht de belastbaarheid van een patiënt dusdanig laag zijn dat zwaardere functionele activiteiten/oefeningen niet mogelijk zijn, dan adviseert de werkgroep om:

- Te starten met krachttraining met laag gewicht of elastiek en flexibiliteitsoefeningen. Het heeft de voorkeur om te starten met isotonische contracties boven isometrische contracties.
- Het bewegingsbereik aan te passen naar wat functioneel nodig is: een volledige beweging is niet nodig.
- Te starten met laag intensieve oefeningen met meer herhalingen en met trainen van de kleine spiergroepen.
- Links en rechts apart (unilateraal) te trainen en spieren geïsoleerd (geen grote spiergroep) te trainen om de cardiopulmonale belasting te verminderen.
- Te starten met één serie met 5-10 herhalingen.
- Licht intensieve training met sterke aandacht voor het vermijden van overbelasting om patiënten vertrouwd te maken met de inspanning en gemotiveerd te houden te overwegen.
- Dagelijks een korte training i.p.v. 2-3 per week een zwaardere training te overwegen.
- Vaker lichte dagelijkse zelfzorg (ADL) activiteiten te laten uitvoeren. Denk aan (het uitlokken van) betekenisvolle bewegingen of basis handelingen zoals zelfstandig naar een bel reiken, tanden poetsen, bril afzetten, haren kammen.

In alle gevallen is het van belang dat er zoveel mogelijk getraind en gemonitord wordt op basis van objectieve trainingsparameters (wattage of hartslag), in combinatie met een subjectieve maat zoals de Borg score (Borg, 1982).

Na het revalidatietraject zal de patiënt naar huis gaan, en eventueel onder begeleiding van een eerstelijns zorgverlener(s) verder trainen en werken aan de participatiedoelen. Het is belangrijk om de patiënten ten tijde van het revalidatietraject al te stimuleren om een actieve en gezonde leefstijl aan te houden. Waar dit

binnen het bereik van de patiënt valt, is het met betrekking tot het bewegen goed om de dosering beschreven in de Beweegrichtlijnen 2017 (Gezondheidsraad, 2017) als uitgangspunt te nemen. De Nederlandse richtlijn verschilt weinig van de internationaal beschikbare richtlijnen (zie o.a. Zaleski, 2016).

Monitoring van training

De werkgroep acht het belangrijk dat gedurende de trainingsperiode structureel wordt nagevraagd of er geen sprake is van overmatige vermoeidheid, benauwdheid, spierpijn en koorts na afloop van een training. Deze aspecten kunnen gemonitord worden met de Borgschaal. Vooral overmatige vermoeidheid lijkt na COVID-19 een frequent voorkomend probleem. Waar nodig moet de trainingsintensiteit aangepast worden en/of meer aandacht te geven aan de energieverdeling over de dag.

Contra-indicaties voor inspanning

Tabel 1 geeft een overzicht van de absolute en relatieve contra-indicaties. Er zijn geen ziekte specifieke contra-indicaties bekend. Wel kan het van meerwaarde zijn om in het geval van comorbiditeit aanvullend de specifieke richtlijnen te raadplegen.

Indien er twijfel is over de belastbaarheid of een pathologische beperking van de inspanningscapaciteit en een functionele test onvoldoende blijkt om hier inzicht in te krijgen, kan de inzet van een CPET worden overwogen (zie ook eerdere opmerkingen). De CPET kan worden gebruikt om te bepalen of er een pathologische beperking bestaat of om een inschatting te maken of de zwaarte van de training aansluit bij de objectieve belastbaarheid van de individuele patiënt.

Tabel 1 Contra-indicatie inspanningstest

Absolute contra-indicaties	Relatieve contra-indicaties

• Een recente significante verandering in het elektrocardiogram in rust suggestief voor ischemie, • recent myocardinfarct(binnen 2 dagen) of een ander acuut cardiaal event, • Instabiele angina pectoris, • Ongecontroleerde hartritmestoornissen die symptomen of hemodynamische problemen veroorzaken, • Symptomatische ernstige aortastenose, • Ongecontroleerd symptomatisch hartfalen, • Acute longembolie of longinfarct, • Acute myocarditis of pericarditis, • Verdacht of bekend aneurysma, • Acute systemische infectie, vergezeld van koorts, pijn in het lichaam of gezwollen lymfeklieren.	• Linker coronaire stenose, • Matige stenotische hartklepaandoening, • Elektrolytafwijkingen (e.g. hypokaliëmie, hypomagnesiëmie), • Ernstige arteriële hypertensie (i.e. systolische bloeddruk van >200 mmHg en/of een diastolische, bloeddruk van >110 mmHg) in rust, • Tachydysritmie of bradydysritmie, • Hypertrofische cardiomyopathie en andere vormen van obstructie van het uitstroomkanaal, • Neuromotorische, musculoskeletale of reumatoïde aandoeningen die worden verergerd door inspanning, • Atrioventriculair blok van hoge graad, • Ventriculair aneurysma, • Ongecontroleerde stofwisselingsziekte (e.g. diabetes, thyrotoxicose, myxoedeem), • Chronische infectieziekte (e.g. Hiv), • Geestelijke of fysieke beperking die leidt tot het onvermogen om voldoende te oefenen. Relatieve contra-indicaties vereisen een beoordeling van arts. Er kan besloten worden om te trainen wanneer de voordelen opwegen tegen de nadelen of risico. Eventueel is training met een verhoogd toezicht niveau mogelijk of een inspanningstest voor de start van de training.

Vertaalde en aangepaste versie van Gibbons (2002).

Waarden en voorkeuren van patiënten (en evt. hun naasten)

Het belangrijkste doel van patiënten binnen de MSR en GRZ is om het dagelijks leven weer op te kunnen pakken, en de activiteiten van het dagelijks leven uit te kunnen voeren zonder overmatige vermoeidheid. Als doelen van de fysieke training noemden patiënten in de enquête het verbeteren van het uithoudingsvermogen, de kracht en controle van de ademhaling (zie de bijlage 'Resultaten enquête onder patiënten').

Hoewel veel patiënten goed gemotiveerd zijn voor de training en zij ook ervaren dat training helpt bij hun revalidatie, kunnen patiënten (zeker in het begin) de training soms als zwaar ervaren. Dit kwam ook nadrukkelijk naar voren uit de enquête. De ervaring van de werkgroep is dat een gedeelte van de patiënten zich tijdens de training soms benauwd voelt en/of rapporteert pijn aan het bewegingsapparaat. Sommige patiënten zullen vermoeidheid ervaren en hierdoor gedurende de rest van de dag zich niet in staat voelen om

nog andere activiteiten op te pakken. Zodra de trainingsperiode vordert, zien we in de praktijk dat veel patiënten positieve effecten ervaren en zich ook beter voelen. Over het algemeen wegen voor de patiënt de voordelen van fysieke training zwaarder dan de nadelen.

Het trainen in een groep kan voor sommige patiënten van toegevoegde waarde zijn, men kan elkaar steunen en stimuleren (zie ook de resultaten van de enquête).

Voor poliklinische patiënten kan het een uitdaging (logistiek) zijn om voor de trainingen naar het revalidatiecentrum of revalidatieafdeling binnen het ziekenhuis te komen.

Kosten (middelenbeslag)

Fysieke training maakt standaard deel uit van de MSR en GRZ, het is niet de verwachting dat het inzetten van fysieke training leidt tot hogere kosten. Wel kan de hoeveelheid gesuperviseerde trainingen van invloed zijn. Daarnaast is het mogelijk dat er bij een subgroep van de patiënten kosten worden gemaakt, vanwege noodzaak om fysieke testen (bijvoorbeeld een CPET) af te nemen. Deze kosten hebben geen invloed op de besluitvorming in deze module.

Aanvaardbaarheid, haalbaarheid en implementatie

Op zich is de zorg aan COVID-19 patiënten binnen de GRZ en MSR vergelijkbaar met andere patiëntengroepen. In bepaalde gevallen kan training met zuurstof nodig zijn (zie de module Zuurstoftherapie; in ontwikkeling).

Er zijn verder geen aspecten op het gebied van de aanvaardbaarheid, haalbaarheid en implementatie die van invloed zijn op de besluitvorming.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Hoewel er nog weinig *evidence* is voor fysieke training bij patiënten die COVID-19 hebben doorgemaakt, is de werkgroep op basis van *evidence* bij andere patiëntenpopulaties en het patiëntenperspectief wel van mening dat fysieke training een onmisbaar onderdeel uitmaakt van een geriatrische of medisch specialistisch revalidatiebehandeling. De werkgroep doet daarom een sterke aanbeveling om te starten met fysieke training. Het is daarbij belangrijk dat de training wordt afgestemd op de met de patiënt bepaalde doelen, de belastbaarheid goed gemonitord wordt en de patiënt ook gemotiveerd wordt om ook na afloop van het revalidatietraject een actieve en gezonde levensstijl aan te houden.

Onderbouwing

Achtergrond

Vermoeidheid en een verminderde fysieke belastbaarheid zijn evident aanwezig na een ernstige COVID-19 infectie. Deze klachten zijn naar verwachting bij een gedeelte van de patiënten onder andere het gevolg van een verminderde fysieke fitheid. De fysieke fitheid neemt bij COVID-19 patiënten af door de infectie en door de periode van immobilisatie gedurende de ziekenhuisopname. De fysieke fitheid kan naar verwachting verbeterd worden met training.

Conclusies / Summary of Findings

Physical fitness (critical)

Very low GRADE	The evidence is very uncertain about the effect of a structural exercise program compared with no structural exercise on physical fitness in patients who have experienced COVID-19. <i>Source: Haameed (2021)</i>

Muscle strength (important)

Very low GRADE	The evidence is very uncertain about the effect of a structural exercise program compared with no structural exercise on muscle strength in patients who have experienced COVID-19. <i>Source: Haameed (2021)</i>

Other outcome measures: physical functioning (critical), quality of life (critical), fatigue (important), physical activity (important), adverse events (important)

- GRADE	The outcome measures physical functioning, quality of life, fatigue, physical activity, and adverse events were not reported in the included studies. <i>Sources: -</i>

Samenvatting literatuurDescription of studies

Hameed (2021) described a prospective cohort study that evaluated whether a virtual rehabilitation program would lead to improvements in strength and cardiopulmonary endurance when compared with no intervention in patients who were discharged home with persistent COVID-19 symptoms. Patients were assigned to either virtual physical therapy (n=44), physical therapy at home (n=25), independent exercise (n=17), or no exercise intervention (n=20). Virtual physical therapy sessions were held via a secure, HIPAA-compliant telehealth platform. The physical therapy consisted of a home exercise guide with a graded, phased exercise program. The length of exercising varied from 30-60 minutes. The average length of follow-up was two weeks. The following outcome measures were reported: change in cardiopulmonary endurance (Step Test Score) and change in lower body strength (Sit-to-Stand score).

Results*Physical fitness (critical)*

Hameed (2021) measured the change in cardiopulmonary endurance by the Step Test Score. The Step Test is measured by counting the number of times the right knee reaches the midway point between patella and iliac crest for a total of two minutes.

- The mean (SD) cardiopulmonary endurance in the virtual physical therapy group improved from 44 (23) times at baseline to 73 (26) times at follow-up (MD 29.0, 95% CI 18.74 to 39.26).
- The mean (SD) cardiopulmonary endurance in the home physical therapy group improved from 46 (27) times at baseline to 71 (30) times at follow-up (MD 25.0, 95% CI 9.18 to 40.82).

- The mean (SD) cardiopulmonary endurance in the independent exercise group improved from 54 (24) times at baseline to 76 (14) times at follow-up (MD 22.0, 95% CI 8.79 to 35.21).
- The mean (SD) cardiopulmonary endurance in the no exercise intervention group improved from 59 (30) times at baseline to 69 (12) times at follow-up (MD 10.0, 95% CI -4.16 to 24.16).

Haameed (2021) did not report differences between the intervention groups and the control group.

Muscle strength (important)

Hameed (2021) measured change in lower body strength by the Sit-to-Stand Score. The Sit-to-Stand test is measured by counting the number of times a patient can stand to a fully erect position from a seated position with arms folded across their chest in 30 seconds time.

- The mean (SD) lower body strength in the virtual physical therapy group improved from 9.0 (4.0) times at baseline to 13.0 (3.0) times at follow-up (MD 4.00, 95% CI 2.52 to 5.48).
- The mean (SD) lower body strength in the home physical therapy group improved from 8.0 (3.0) times at baseline to 12.0 (1.0) times at follow-up (MD 4.00, 95% CI 2.76 to 5.24).
- The mean (SD) lower body strength in the home independent exercise group improved from 10.0 (5.0) times at baseline to 13.0 (3.0) times at follow-up (MD 3.00, 95% CI 0.23 to 5.77).
- The mean (SD) lower body strength in the no exercise intervention group decreased from 12.0 (4.0) times at baseline to 11.0 (7.0) times at follow-up (MD 4.00, 95% CI 2.76 to 5.24).

Haameed (2021) did not report differences between the intervention groups and the control group.

Other outcome measures: physical functioning (critical), quality of life (critical), fatigue (important), physical activity (important), adverse events (important)

Haameed (2021) did not report information regarding these outcome measures.

Level of evidence of the literature

Physical fitness

The level of evidence started as low because the study was an observational study. The level of evidence regarding the outcome measure physical fitness was downgraded by one level because of study limitations (risk of bias) and the inclusion of a single study with a limited number of patients included (imprecision). The level of evidence of the outcome 'physical fitness' is *very low*.

Muscle strength

The level of evidence started as low because the study was an observational study. The level of evidence regarding the outcome measure muscle strength was downgraded by one level because of study limitations (risk of bias) and the inclusion of a single study with a limited number of patients included (imprecision). The level of evidence of the outcome 'muscle strength' is *very low*.

The level of evidence of the other outcome measures (physical functioning, quality of life, fatigue, physical activity, adverse events) was not assessed due to lack of studies.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the beneficial and unfavorable effects of a structural (physical) exercise program in patients who have experienced COVID-19?

P: Patients who have experienced COVID-19.

I: Structural (physical) exercise program.

C: Usual care/ other (physical) exercise programs (yoga, mobilization exercises, personal advice).

O: Physical functioning, quality of life, physical fitness, muscle strength, fatigue, physical activity, adverse events.

Relevant populations

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients during the acute phase who received the intervention in the intensive care or a hospital ward, are excluded.

Relevant outcome measures

The guideline development group considered physical functioning, quality of life and physical fitness as critical outcome measures for decision making; and muscle strength, fatigue, physical activity and adverse events as important outcome measures for decision making.

The working group defined the outcome measures as follows:

- Physical functioning: as determined with a validated physical performance test (e.g., the 6-minute walk test). Subscales of quality of life questionnaires were not included.
- Quality of life: as determined with a validated quality of life questionnaire (e.g., 36-item Short Form Health Survey, EuroQol-5D).
- Physical fitness: as determined with a cardiopulmonary exercise test (CPET) or submaximal exercise test.
- Muscle strength: as assessed using dynamometry or as expressed as the one repetition maximum.
- Fatigue: as assessed using a validated fatigue questionnaire (e.g., Fatigue Severity Scale, Modified Fatigue Impact Scale).
- Physical activity: as determined with accelerometry or pedometry.

The working group did not predefine the outcome measure adverse events, but used the definitions used in the included studies.

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Given the variety in methods to determine and report adverse events, the working group did not a priori define the minimal clinically (patient) important difference for this outcome measure. The differences between the groups were evaluated by the working group after data extraction.

Search and select (Methods)

The databases Medline (via OVID), Embase (via Embase.com) and CINAHL were searched with until 2 March 2021. The search strategy was broadened on 30 March 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1,924 hits. Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above.

Two studies were initially selected based on title and abstract screening. After reading the full text, one study was excluded (see the table with reasons for exclusion under the tab Methods), and one study was included.

Results

One study was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 24-09-2021

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Ademoefeningen en ademspiertraining binnen de MSR/GRZ na COVID-19

Uitgangsvraag

Wat is de (toegevoegde) waarde van ademoefeningen en/of ademspiertraining bij patiënten die COVID-19 hebben doorgemaakt en behandeld worden binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg?

Aanbeveling

Ademoefeningen

Zet binnen de medisch specialistische revalidatie en geriatrische revalidatiezorg ademoefeningen in bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van:

- dyspneu; en/of
- een disfunctioneel ademhalingspatroon; en/of
- dysfunctie van het middenrif/diafragma.

Ademspiertraining

Bepaal de ademspierkracht bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van dyspneu.

Binnen de medisch specialistische revalidatie

Zet ademspiertraining in bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van:

- ademspierzwakte (zie Tabel 1); en
- klachten van dyspneu; en
- geen contra-indicaties*.

Binnen de geriatrische revalidatiezorg

Overweeg ademspiertraining in te zetten bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van:

- ademspierzwakte (zie Tabel 1); en
- klachten van dyspneu; en
- geen contra-indicaties*.

Stem de dosering af op de belastbaarheid van de patiënt. De volgende dosering zou als startpunt kunnen dienen:

- Frequentie: 3 tot 5 dagen in de week, twee keer per dag 30 ademteugen (eventueel te verdelen in 3x10 of 2x15 ademteugen).
- Intensiteit: weerstand van 30% van de maximale inademingsdruk (Pi-max) met een ervaren mate van

vermoeidheid op de 10-punts Borgschaal van 3 tot 4.

- Tijd: 2x 30-ademteugen per sessie.
- Type: Threshold loading: constant pressure of variable pressure.

** De contra-indicaties voor ademspiertraining zijn:*

- *spontane pneumothorax in voorgeschiedenis;*
- *blessure of een recente operatie (<6-8 weken) waardoor training niet mogelijk is;*
- *astma met regelmatige onverwachte (en zware) exacerbaties;*
- *recent myocard infarct of andere trombo-embolische aandoeningen;*
- *aneurysma;*
- *koorts > 38 graden of hoger;*
- *recente of niet-volledige herstelde trommelvliesperforaties en/of KNO-infecties.*

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er zijn twee studies die het effect van kortdurende (twee tot zes weken follow-up) respiratoire revalidatie hebben geëvalueerd bij patiënten na een COVID-19 infectie. In deze studies is sprake van een hoog risico op bias en een beperkt aantal deelnemende patiënten. De bewijskracht voor de gerapporteerde uitkomstmaten (dyspneu, fysiek functioneren en kwaliteit van leven) en de overall bewijskracht komt daarmee op zeer laag. Hier ligt duidelijk een kennislacune.

Ondanks de beperkte literatuur, is de werkgroep op basis van *expert opinion* van mening dat adem oefeningen en ademspiertraining binnen de medische specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ) bij specifieke patiëntgroepen een plaats hebben. We lichten dit hieronder toe.

Ademoefeningen

Bij ademproblemen kan een patiënt een dyspneugevoel of het gevoel niet goed te kunnen doorademen ervaren. Soms is sprake van te veel, te snel of te oppervlakkig ademhalen (disfunctioneel ademen). De werkgroep is van mening dat binnen de MSR en GRZ ademoefeningen behulpzaam kunnen zijn met betrekking tot het verminderen van de dyspneuklachten bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van dyspneu, een disfunctioneel adempatroon en/of dysfunctie van het middenrif/diafragma.

Aangezien bij patiënten die COVID-19 hebben doorgemaakt (in de revalidatiefase) meestal geen sprake is van sputum dat opgehoest hoeft te worden, is de voorkeur om ademoefeningen uit te voeren die gericht zijn op een diafragmale ademhaling (buikademhaling). Patiënten worden geadviseerd diafragmaal te ademen om de buikademhaling te verdiepen in combinatie met het vergroten van de thoracale expansie. Zodoende wordt de elastische en mechanische weerstand van het ademen kleiner waardoor het ademhalen minder energie gaat kosten (Ho, 2000). Het is belangrijk dat de therapeut die de ademoefeningen geeft zich bewust

is van, en alert is op, mogelijke mentale spanning. Ontspanningsoefeningen in combinatie met adem oefeningen kunnen mogelijk een rol spelen bij het verminderen van de mentale spanning, en daarmee op natuurlijk wijze de diafragmale ademhaling vergroten.

Ademspiertraining

In tegenstelling tot adem oefeningen die met minimale weerstand en inspanning worden uitgevoerd, is ademspiertraining een vorm van krachttraining. Deze training is vooral geschikt voor patiënten met verminderde kracht/power van de ademspieren (zie Tabel 1). Bij ademspiertraining wordt de patiënt eveneens geïnstrueerd om een diepe diafragmale ademhaling uit te voeren maar nu tegen een weerstand. Hiervoor worden meestal de apparaten 'Threshold IMT', 'POWERbreathe Medic' of 'POWERbreathe Plus Medic' gebruikt (Menzes, 2018). Begeleiding door een bekwame fysiotherapeut wordt sterk geadviseerd, zodat de training adequaat uitgevoerd wordt en de juiste intensiteit gewaarborgd wordt.

Ademhalingsspiertaining lijkt positieve effecten te hebben bij verschillende patiëntenpopulaties (zie bijvoorbeeld Chuang, 2017, Gosselink, 2011, Lisboa, 1994, Medeiros, 2019). Echter, zelfs bij gezonde personen zonder dyspneuklachten is aangetoond dat training van de ademhalingsspieren lichte voordelen oplevert voor de trainingsprestaties (Illi, 2012). Bij conventionele trainingsprotocollen voor ademhalingsspieren is ademen door een apparaat vereist waarin de weerstand met een klep makkelijk en betrouwbaar in te stellen is. Zodra er voldoende (inspiratoire of expiratoire) druk is gegenereerd, gaat de klep open en stroomt er lucht door het apparaat. Een percentage van de maximale inademiingsdruk (Pi-max) of maximale uitademiingsdruk (Pe-max) wordt gebruikt als trainingsbelasting (intensiteit).

De werkgroep raadt ademhalingsspiertaining aan bij patiënten binnen de MSR en GRZ die COVID-19 hebben doorgemaakt en bij wie er sprake is van:

- ademspierzwakte (zie Tabel 1); en
- klachten van dyspneu; en
- afwezigheid van contra-indicaties (zie onderstaand).

Het is hierbij wel mogelijk dat bij patiënten binnen de GRZ ademspiertraining als onderdeel van de revalidatie niet altijd de hoogste prioriteit heeft.

Internationaal zijn er richtlijnen (bijvoorbeeld van de European Respiratory Society; Laveneziana, 2019) beschikbaar waarin testprocedures van de ademhalingsspieren worden beschreven. Hiernaast zijn er criteria en drempelwaarden voorgesteld voor het definiëren van zwakte van de ademhalingsspieren. De werkgroep raadt aan om deze richtlijnen te volgen en de drempelwaarden uit Tabel 1 aan te houden bij de evaluatie of er sprake is van ademspierzwakte.

Tabel 1 Drempelwaarde ademspierzwakte*

Leeftijd (in jaren)	Drempelwaarde (in cm H ₂ O)	
	Mannen	Vrouwen
< 40	63	58
40 tot 60	55	50
61 tot 80	47	43
> 80	42	38

***Waarden overgenomen uit Laveneziana (2019).**

Deze waarden representeren de maximale inademiingsdruk die geassocieerd wordt met een hogere waarschijnlijkheid dat er sprake is van ademspierzwakte.

Er zijn een aantal contra-indicaties voor ademspiertraining bekend (Laveneziana, 2019). De werkgroep raadt aan om ook bij patiënten die COVID-19 hebben doorgemaakt rekening te houden met de volgende contra-indicaties voor ademspiertraining:

- spontane pneumothorax in voorgeschiedenis;
- blessure of een recente operatie (<6-8 weken) waardoor training niet mogelijk is;
- astma met regelmatige onverwachte (en zware) exacerbaties;
- recent myocard infarct of andere trombo-embolische aandoeningen;
- aneurysma;
- koorts > 38 graden of hoger;
- recente of niet-volledige herstelde trommelvliesperforaties en/of KNO-infecties.

Bij aanwezigheid van één of meerdere contra-indicaties moet worden afgezien van ademhalingspiettraining.

De aan te bieden ademspiertraining moet voldoen aan het FITT-principe. Hierbij lijkt het belangrijk om zowel duurtraining (flow genererend, hoge snelheid, lage weerstand) als krachttraining (druk genererend, hoge weerstand, lage snelheid) op te nemen in het programma. De dosering wordt idealiter afgestemd op de belastbaarheid van de patiënt en op de uitvoer en gedoseerde opbouw van de dagelijkse activiteiten. Na instructie van de training kan de patiënt veelal zelf met de training aan de slag. Het wordt aangeraden om de belastbaarheid een keer per twee weken in gesuperviseerde trainingen te evalueren met behulp van een monddrukmeting. Als startpunt van de trainingen kan de volgende dosering worden overwogen:

- Frequentie: 3 tot 5 dagen in de week, twee keer per dag 30-ademteugen (eventueel te verdelen in 3x10 of 2x15 ademteugen).
- Intensiteit: weerstand van 30% van de maximale inademiingsdruk (P_{imax}) bij een *constant pressure threshold* en 40-50% van de maximale inademiingsdruk (P_{imax}) bij *variable pressure threshold* met een ervaren mate van vermoeidheid op de 10-punts Borgschaal van 3 tot 4.
- Tijd: 2x per dag 30 ademteugen.
- Type: Threshold loading: constant pressure of variable pressure.

Waarden en voorkeuren van patiënten (en eventueel hun naasten)

Voor patiënten is het belangrijk om de ademhaling onder controle te hebben en geen benauwdheid te

ervaren. De verwachting is dat de meeste patiënten positief staan tegen de inzet van deze adem oefeningen en ademspiertraining.

Kosten (middelenbeslag)

Er is geen informatie beschikbaar met betrekking tot de kosteneffectiviteit van de interventies. De kosten worden gemaakt voor de gesuperviseerde behandelingen door een paramedicus, het bepalen of er sprake is van spierzwakte en het gebruik van apparatuur (in het geval van ademspiertraining). Voor het vaststellen/meten van ademspierzwakte moeten zowel de inspiratoire als expiratoire monddrukken worden gemeten. Hiervoor is apparatuur om monddrukken te meten nodig. Er zijn verschillende trainingsapparaten voor het trainen van de inspiratoire en expiratoire ademspieren op de markt, waarbij de prijs varieert tussen de 30 en 300 euro. De goedkopere opties voldoen. Deze trainingsapparaten zijn niet voor meerdere patiënten te gebruiken. De kosten voor de interventies worden vergoed zolang zij onderdeel uitmaken van de MSR of GRZ behandeling. De trainingsapparatuur wordt meestal door de instelling voor MSR of GRZ aangeschaft.

Aanvaardbaarheid, haalbaarheid en implementatie

Er zijn verschillende specialismen die de patiënt bij de adem oefeningen en ademspiertraining kunnen begeleiden. Bij de behandeling van COVID-19 patiënten is het belangrijk dat voldoende kennis en kunde op dit gebied binnen het revalidatiecentrum beschikbaar is. Naar verwachting is dit binnen de MSR geen probleem. Mogelijk is nog niet in alle GRZ-instellingen de apparatuur om monddrukken te meten en de kennis en kunde om de ademspiertraining te begeleiden voldoende aanwezig. Ten aanzien van aanvaardbaarheid, haalbaarheid en implementatie zijn er verder geen overwegingen die van invloed zijn op de besluitvorming.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Aanbeveling Adem oefeningen

Ondanks dat de literatuur op dit onderwerp nog zeer beperkt is, is de werkgroep van mening dat bij patiënten die COVID-19 hebben doorgemaakt en bij wie er sprake is van dyspneu, een disfunctioneel ademhalingspatroon en/of dysfunctie van het middenrif/diafragma adem oefeningen ingezet moeten worden. Patiënten zijn naar verwachting positief over de inzet van de oefeningen. De werkgroep kiest daarom, ondanks de lage bewijskracht, voor een sterke aanbeveling met betrekking de inzet van deze interventie.

Aanbeveling Ademspiertraining

Hoewel er (nog) geen literatuur beschikbaar is, is het advies van de werkgroep van om bij patiënten die COVID-19 hebben doorgemaakt en klachten hebben van dyspnoe standaard de ademspierkracht te meten/bepalen. Indien er bij deze patiënten sprake is van ademspierzwakte en er geen contra-indicaties zijn, wordt ademspiertraining aanbevolen. Vanuit andere patiëntengroepen is bekend dat ademspiertraining positieve effecten kan hebben. De werkgroep kiest, ondanks de lage bewijskracht, voor een sterke aanbeveling met betrekking tot de inzet van deze interventie binnen de MSR. Voor de GRZ is gekozen voor een zwakke aanbeveling in verband met beperkte beschikbaarheid van expertise en apparatuur en mogelijk andere prioritering van behandeldoelen. Met betrekking tot de dosering van de oefeningen wordt uitgegaan

van eerdere ervaringen bij andere patiëntpopulaties, maar uiteraard is het hierbij belangrijk om de belastbaarheid van de individuele patiënt goed in ogenschouw te houden. Belangrijk is om de dosering ook af te stemmen op de uitvoer en gedoseerde opbouw van de dagelijkse activiteiten.

Onderbouwing

Achtergrond

Dyspneu is een veelvoorkomende klacht na COVID-19 infectie (NICE, 2020). Dyspneuklachten kunnen voorkomen bij pulmonale afwijkingen, bij een snel en oppervlakkig adempatroon (een disfunctionele ademhaling) of als er onvoldoende kracht en/of uithoudingsvermogen is van de ademhalingspijpen. Adem oefeningen of ademspiertraining zouden kunnen zorgen voor een afname van dyspneu en toename van de inspanningstolerantie, en op deze wijze patiënten kunnen helpen om de fysieke inspanningen beter te tolereren en sneller vooruitgang te boeken.

Een disfunctionele ademhaling kan ook leiden tot stemproblemen, waarvoor adem – en stemoefeningen geïndiceerd kunnen zijn. Dit onderwerp valt echter buiten de afbakening van de huidige richtlijn(module). Voor stemproblematiek verwijzen we naar de richtlijn [Stemklachten](#) (NVKNO, 2016)

Conclusies / Summary of Findings

1. Dyspnea (critical)

Very low GRADE	The evidence is very uncertain about the effect of a respiratory rehabilitation program on dyspnea. <i>Sources: (Abodonya, 2021)</i>

2. Physical functioning (critical)

Very low GRADE	The evidence is very uncertain about the effect of a respiratory rehabilitation program on physical functioning. <i>Sources: (Liu, 2020; Abodonya, 2021)</i>

3. Quality of life (important)

Very low GRADE	The evidence is very uncertain about the effect of a respiratory rehabilitation program on quality of life. <i>Sources: (Liu, 2020; Abodonya, 2021)</i>

4-5. Respiratory muscle strength (important) and participation (important)

- GRADE	The outcomes were not reported in the included studies.

Samenvatting literatuur

Description of studies

Liu (2020) describes a quasi-randomized controlled trial evaluating the effects of a respiratory rehabilitation program after hospital discharge for COVID-19 patients aged 65 years and older without COPD. A total of 76 patients participated in the study, 38 were allocated to the rehabilitation group and 38 to the no intervention (control) group. The rehabilitation program consisted of six weeks of (1) expiratory muscle training; (2) cough exercise; (3) diaphragmatic breathing training; (4) stretching exercise; and (5) home exercise. Respiratory rehabilitation consisted of two sessions per week for six weeks, once a day for ten minutes. Relevant outcome measures included physical functioning (six-minute walk test and Functional Independence Measure; FIM scores) and quality of life (36-item Short Form Health Survey; SF-36). Data were analysed using the Mann Whitney U test. Four patients were lost to follow-up (unable to continue rehabilitation), two in each study arm.

Abodonya (2021) performed a prospective pilot control clinical study to assess the efficacy of inspiratory muscle training (IMT) on recovered COVID-19 patients following mechanical ventilation. A total of 42 patients participated in the study, 21 were allocated to the IMT-group and 21 were allocated to the control group. All patients were recruited from the ICU and selected depending on their availability rather than the calculation of the sample size and power analysis. Although patients were included from the ICU, the exact location of the intervention is unclear. Hence, we decided to include this study. Both groups have received an incentive spirometer exercise. After weaning from mechanical ventilation, each patient was instructed to perform incentive breathing exercise in a relaxed sitting position two times daily for two weeks. In the IMT-group, patients received additionally a program of IMT using a threshold inspiratory muscle trainer and consisting of two sessions daily, five days a week for two weeks. Each session consisted of six inspiratory cycles with a threshold load of 50% of the maximal inspiratory pressure (MIP). Each cycle consisted of five minutes of resisted inspiration followed by one minute rest time. Follow-up period was two weeks in total for both groups.

Relevant outcomes included physical functioning (six-minute walk test), dyspnea (Dyspnea Severity Index, DSI), and quality of life (EQ-5D-3L). Outcomes were assessed before starting the study intervention and immediately after intervention. No lost to follow-up or missing data was reported.

Results

1. Dyspnea (critical)

This outcome measure was only included in Abodonya (2021). Abodonya (2021) reported a statistically significant and clinically relevant difference in dyspnea measured with the DSI, favouring the IMT-group. In the IMT-group, dyspnea decreased from 18.5 ± 4.3 to 14.2 ± 3.5 whereas the control-group decreased from 17.8 ± 5.1 to 17.1 ± 4.8 at two weeks follow-up (between-group difference $p=0.032$).

2. Physical functioning (critical)

Both studies (Liu, 2020; Abodonya, 2021) reported on the outcome physical functioning. Liu (2020) reported a statistically significant and clinically relevant difference in the walking distance during the 6-minute walk test between the intervention-group (mean $\pm$ SD: 212.3 ± 82.5 m) and the control-group (mean $\pm$ SD: 157.2 ± 71.7 m) after six weeks, in favour of the intervention-group. In addition, physical function was measured with the Functional Independence Measure (FIM) scale; no significant improvements over time or between groups were reported.

Abodonya (2021) reported a statistically significant and clinically relevant difference in the walking distance during the 6-minute walk test, favouring the IMT-group. In the IMT-group the distance increased from 332.6 ± 34.5 m to 376.5 ± 39.4 m whereas the control group increased from 329.7 ± 37.8 m to 334.8 ± 38.2 m at two weeks follow-up (between-group difference $p=0.028$).

3. *Quality of life (important)*

Both studies (Liu, 2020; Abodonya, 2021) reported on the outcome quality of life. Liu (2020) reported that at six weeks, the intervention scored statistically significant better on all eight dimensions of the SF-36 compared to the control group. For instance, after six weeks the mean $\pm$ SD of the physical health subscale was 71.6 ± 7.6 in the intervention group and 54.1 ± 7.5 in the control group, while baseline values were almost identical (52.4 ± 6.2 versus 53.2 ± 7.7). The differences between the groups are considered clinically relevant.

Abodonya (2021) reported a statistically significant and clinically relevant difference in the total score of total score of the EQ-5D-3L, favouring the IMT-group. In the IMT-group, quality of life increased from 38.6 ± 5.8 to 59.4 ± 8.3 whereas the control-group increased from 40.7 ± 6.2 to 43.3 ± 6.5 at two weeks follow-up (between-group difference $p=0.021$). The differences between the groups are considered clinically relevant.

4-5. *Respiratory muscle strength (important), and participation (important)*

These outcome measures were not included in Liu (2020) and Abodonya (2021).

Level of evidence

The level of evidence regarding the outcome dyspnea started at low as it was based on a control clinical study but was downgraded to *very low* due to study limitations (risk of bias, -1) and the inclusion of a single study with a small study population (imprecision, -1).

The level of evidence regarding the outcome physical functioning started at high as a quasi-randomised study was included but was downgraded by three levels to *very low* due to study limitations (risk of bias, -2) and the relatively small number of included patients (imprecision, -1).

The level of evidence regarding the outcome quality of life started at high but was downgraded by three levels to *very low* due to study limitations (risk of bias, -2), and the relatively small number of included patients (imprecision, -1).

The level of evidence regarding the outcome measures respiratory muscle strength and participation were not assessed due to lack of studies.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the beneficial and unfavourable effects of breathing exercises or respiratory rehabilitation in patients who have experienced COVID-19?

P: patients who have experienced COVID-19.

I: respiratory muscle training/ breathing exercises/ respiratory rehabilitation.

C: placebo/ usual care/ other types of interventions (e.g., yoga, relaxation).

O: dyspnea, physical functioning, quality of life, respiratory muscle strength, participation.

Relevant populations

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients during the acute phase who received the intervention in the intensive care or a hospital ward, are excluded.

Relevant outcome measures

The guideline development group considered dyspnea and physical functioning as a critical outcome measure for decision making; and quality of life, respiratory muscle strength, and participation as an important outcome measure for decision making.

The working group defined the outcome measures as follows:

- Dyspnea: as determined using a validated instrument, assessed at rest, during exercise, and/or during speech.
- Physical functioning: as determined with a validated physical performance test or validated questionnaires.
- Quality of Life: as determined with a validated quality of life questionnaire (for example 36-item Short Form Health Survey, EuroQol-5D).
- Respiratory muscle strength: as expressed as the Pi-max and/or Pe-max.
- Participation: as determined with a validated participation questionnaire.

The working group defined three points on the SF-36 PCS and three points on the SF-36 MCS (Frendl, 2014) as a minimal clinically (patient) important difference. For all other outcomes, the working group defined an increase of 10% of the mean or median in comparison with the baseline value of the study groups as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID), Embase (via Embase.com), and Cinahl (via Ebsco.com) were searched with relevant search terms until April 28th, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 390 hits. Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above. Six studies were initially selected based on title and abstract screening. After reading the full text, four studies were excluded (see the table with reasons for exclusion under the tab Methods), and two studies were included.

Results

Two studies were included in the analysis of the literature. Important study characteristics and results are

summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 24-09-2021

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Meetinstrumenten binnen de MSR/GRZ

Uitgangsvraag

Welke domeinen moeten in kaart gebracht worden voor de evaluatie van de gezondheidsstatus van patiënten die COVID-19 hebben doorgemaakt en behandeld worden binnen de medisch specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ)? En welke meetinstrumenten en/of vragenlijsten zouden hiervoor gebruikt kunnen worden?

Aanbeveling

Breng de domeinen zoals beschreven in tabel 1 in kaart om de gezondheidsstatus van patiënten met COVID-19 binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg te evalueren.

Gebruik hierbij gestandaardiseerde en gevalideerde vragenlijsten en meetinstrumenten. Voorbeelden zijn hier gepresenteerd, dit betreft geen uitputtende opsomming.

Houd bij de keuze voor vragenlijsten en meetinstrumenten rekening met:

- Het individueel in kaart brengen van patiënten in voor de patiënt relevante domeinen.
- De (fysieke en mentale) belastbaarheid van patiënten.
- Het minimaliseren van redundantie in meetinstrumenten.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er zijn geen systematische reviews gevonden waarin de psychometrische eigenschappen zijn onderzocht van meetinstrumenten waarmee eventueel de gezondheidsstatus van patiënten in kaart zou kunnen worden gebracht. Daarnaast zijn er geen internationale richtlijnen of publicaties gevonden waarin specifieke klinimetriesets voor deze groep patiënten zijn vergeleken.

Gezien het grillige en onvoorspelbare beloop en de soms lange periode van herstel bij COVID-19, pleit de werkgroep voor een integrale benadering van de patiënt. Hierbij is niet alleen het somatisch functioneren belangrijk, maar ook de psychische, cognitieve en sociale aspecten. Vanwege de afwezigheid van literatuur, kiest de werkgroep ervoor om aanbevelingen te formuleren over welke domeinen gemeten zouden moeten worden, en niet om strikt een set meetinstrumenten voor te schrijven. Er worden wel voorbeelden gegeven van meetinstrumenten die gebruikt zouden kunnen worden in de praktijk.

De werkgroep raadt aan om de domeinen zoals beschreven in Tabel 1 in kaart te brengen.

Voor het bepalen van de domeinen zijn we uitgegaan van de verschillende domeinen die in generalistische beroepsgroepen gebruikt worden (NVKG, 2010; Verenso 2020; VRA 2020). Het patroon en de diversiteit van de klachten en functiestoornissen die internationaal uitgebreid beschreven zijn tijdens het beloop van het herstel na COVID-19 (Lopez-Leon, 2021) zijn leidend geweest bij de keuze van de relevante domeinen. Als methode voor het indelen van de verschillende domeinen is de International Classification of Functioning,

Disability and Health (ICF) gebruikt (WHO, 2001). Het ICF-model bestaat uit een raamwerk van classificaties die tezamen een gestandaardiseerd begrippenkader vormen voor het beschrijven van het menselijk functioneren en de problemen die daarin kunnen optreden. In dit model wordt het functioneren van de patiënt beschreven vanuit verschillende perspectieven (zoals anatomische eigenschappen, activiteiten, participatie).

Tabel 1 Domeinen die in kaart gebracht moeten worden bij patiënten die COVID-19 hebben doorgemaakt.

Domein	Perspectief	Items	Sub-items
Functies en anatomische eigenschappen	Hierbij gaat het om het perspectief van het menselijk organisme (orgaansystemen).	Mentale functies en anatomische eigenschappen	Algemene mentale functies (moeheid)
			Specifieke mentale functies (cognitie)
			Specifieke mentale functies (stemming)
			Specifieke mentale functies (post-traumatische stress)*
		- Zenuwstelsel: - Sensorische functie en (neuropatische) pijn - Tremoren	Pijn
		Slik, spraak- en stemfuncties	Specifieke orofaryngeale functies als tongkracht, larynxheffing, slikreflex en algemene mondmotoriek
		Functies gerelateerd aan het hart- en bloedvatenstelsel, hematologisch, afweer en ademhalingsstelsel	Ademhaling, functies van ademhalingsspieren Andere functies en gewaarwordingen van hart, bloedvatenstelsel en ademhalingsstelsel (dyspnoe, inspanningstolerantie)

		• Functies gerelateerd aan spijsvertering, metabool- en hormoonstelsel.	Functies van spijsverteringsstelsel, screening voedingstoestand
			Lichaamssamenstelling (vetvrije massa)
		• Functies gerelateerd aan bewegingssysteem	Spierfuncties
Activiteiten en participatie	Dit betreft het perspectief van het menselijk handelen en de mate van als deelnemer aan het maatschappelijke leven.	• Leren en toepassen van kennis	Leren en toepassen van kennis
		• Algemene taken en eisen	Gedrag objectief
			Gedrag subjectief
			Ondernemen van taken en omgaan met stress
		• Communicatie	Begrijpen, zich uiten
		• Mobiliteit	Lopen, zich verplaatsen, manipuleren
		• Zelfverzorging	Algemene dagelijkse levensverrichtingen
		• Huishoudelijke taken	Huishouden, bijvoorbeeld het bereiden van maaltijden.
		• Tussenmenselijke interacties en relaties	Mantelzorgbelasting
		• Belangrijke levensgebieden	Opleiding, beroep.

		• Maatschappelijk, sociaal en burgerlijk leven	Sociaal functioneren
Externe factoren	Externe factoren bevatten de fysieke en sociale omgeving waarin mensen leven, deze factoren kunnen een positieve of negatieve invloed hebben op alle componenten van het functioneren en de problemen daarmee.	• Producten en technologie, natuurlijke omgeving, ondersteuning en relaties, attitudes, diensten/systemen en beleid	
Persoonlijke factoren	Persoonlijke factoren betreffen de individuele achtergrond van het leven van een individu en bestaan uit kenmerken van het individu die géén deel uitmaken van de functionele gezondheidstoestand.	• Acceptatie • Levensstijl	Acceptatie en verwerking beperkingen dagelijks leven (bijvoorbeeld ontkenning, verzet, verdriet, acceptatie)
		• Algemene tevredenheid	Algemene tevredenheid
		• Copingstijl	Reacties op stress of een probleem
		• Zelfeffectiviteit	Vertrouwen in eigen bekwaamheid/oplossend vermogen

Als methode voor het indelen van de verschillende domeinen is de International Classification of Functioning, Disability and Health (ICF) gebruikt (WHO, 2001).

In de bijlage van deze module doet de werkgroep een aantal suggesties voor gevalideerde meetinstrumenten en vragenlijsten waarmee deze domeinen in kaart kunnen worden gebracht tijdens het intake-assessment, het beoordelen van de voortuitgang van revalidatie en bij de overdracht naar huisarts of andere instelling. Hoewel geen van deze vragenlijsten specifiek gevalideerd zijn voor patiënten die COVID-19 hebben doorgemaakt en behandeld worden binnen de medisch specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ), zijn er op het eerste gezicht geen concrete redenen dat ze niet geschikt zouden zijn bij deze patiëntengroep. Veel van deze meetinstrumenten worden reeds breed gebruikt binnen de MSR en GRZ en het Elektronisch

Patiënten Dossier (EPD) is hier vaak op ingericht. Hoewel er variatie is tussen meetinstrumenten, is de (tijds)belasting van de individuele meetinstrumenten redelijk beperkt, zijn de resultaten/eindscores eenduidig te interpreteren en zijn er veelal normwaarden beschikbaar.

Zoals uit de bijlage blijkt, zijn er voor de meeste domeinen meerdere opties beschikbaar. Bij de samenstelling van de set meetinstrumenten is het belangrijk om rekening te houden met de volgende punten:

- Als een meetinstrument gebruikt wordt om te monitoren hoe iemand op een behandeling reageert, moeten er per individu relevante domeinen geïdentificeerd worden. Als testen te intensief blijkt kunnen observaties van het dagelijks handelen (het liefst in de eigen context) gebruikt worden als screening en dynamisch meetinstrument waar interventies op gebaseerd kunnen worden.
- Houd rekening met de individuele (fysieke en mentale) belastbaarheid van de patiënt en eventueel aanwezige vertraagde reactie op overbelasting.
- Bij de ontwikkeling van een set meetinstrumenten kan het samenvoegen van domeinen leiden tot redundantie (overtolligheid/ overbodigheid), waardoor een vragenlijst onnodig veel te lang wordt en weinig verschillende aspecten meet.

Mochten er andere meetinstrumenten niet in de lijst gerapporteerd staan maar wel geschikt lijken, dan is het belangrijk dat de psychometrische eigenschappen (validiteit, betrouwbaarheid en responsiviteit) in acht genomen wordt voordat de meetinstrumenten in de praktijk gebruik worden.

Voorbeelden van vragenlijsten die domein overstijgend ingezet kunnen worden zijn de Nijmegen Clinical Screening Instrument (NCSI) en de Utrechtse Schaal voor de Evaluatie van Klinische Revalidatie (USER). Het NCSI is een samengestelde set van (onderdelen van) bestaande gevalideerde vragenlijsten en brengt integrale gezondheidstoestand in kaart (Peters, 2009). De USER is een meetinstrument om het resultaat van de klinische revalidatie te meten, waarbij wordt gemeten hoe zelfredzaam iemand is op het gebied van mobiliteit, zelfverzorging en cognitie (Post, 2009).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Voor patiënten is het belangrijk om zo spoedig en volledig mogelijk te herstellen van COVID-19. Uit de resultaten van de patiëntenquête blijkt dat testen veelal in het begin, tijdens en aan het einde van het revalidatietraject worden afgenomen (zie de bijlage '[Resultaten enquête onder patiënten](#)'). De respondenten ervaren de testen die afgenomen werden in het kader van revalidatie vaak als goed of als zwaar. Té zwaar of té makkelijk is niet genoemd. Het bespreken van de uitslag van de test met de patiënt wordt door de meeste patiënten ervaren als meerwaarde, het kan de patiënt meer inzicht geven en kan motiverend werken.

Patiënten hebben naar verwachting baat bij vaststellen van het pre-morbide niveau van functioneren en participatie. Door vervolgens een breed scala aan aspecten van gezondheidsstatus te evalueren vooraf, gedurende en na de medisch specialistische revalidatie of geriatrische revalidatiezorg, krijgen patiënt en behandelaar inzicht in de vooruitgang van de patiënt gedurende het revalidatietraject. De uitkomsten van de meetinstrumenten kunnen zo een therapeutisch doel dienen: door het stellen van einddoelen kan patiënt toewerken naar verbetering ten opzichte van een startpunt. Daarnaast is het voor de behandelaar mogelijk om met de resultaten uit de meetinstrumenten de interventies meer op maat te maken, zodat deze nog

beter aansluit bij de behoefte van de patiënt.

Kosten (middelenbeslag)

Op het gebied van kosten worden er geen noemenswaardige voordelen of bezwaren gezien die van invloed zijn op de besluitvorming. De aanschaf van gevalideerde meetinstrumenten en vragenlijsten kan theoretisch gezien kosten met zich meebrengen. Echter, deze kosten zijn uiterst laag in vergelijking met andere benodigde faciliteiten voor behandeling van patiënten met doorgemaakte COVID-19 binnen de MSR/GRZ en personeelskosten van zorgverleners.

Aanvaardbaarheid, haalbaarheid en implementatie

Binnen de GRZ/MSR is het gebruikelijk om te werken met meetinstrumenten. Echter, vanuit het werkveld was er behoefte om het klinisch beeld en het beloop van COVID-19 meer uniform in kaart te brengen. Bij aanvang, tijdens en bij afsluiting van de behandeling kunnen de meetinstrumenten worden gebruikt om het beloop te evalueren. De afname meetinstrumenten en vragenlijsten is tegenwoordig steeds meer verweven met de mogelijkheden in het EPD. Dit kan tijdsbesparing en een efficiëntere werkwijze opleveren. Daarentegen blijft de balans cruciaal tussen de beschikbare behandeltijd per patiënt en de tijdsinvestering van de afname van meetinstrumenten en vragenlijsten.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Hoewel er nog weinig evidentie is met betrekking tot de klinimetrische eigenschappen van meetinstrumenten bij patiënten die COVID-19 hebben doorgemaakt en er in internationale richtlijnen nog geen set van meetinstrumenten is beschreven, is de werkgroep wel van mening dat het in kaart brengen van specifieke domeinen een onmisbaar onderdeel uitmaakt van de MSR en GRZ. Naast de aanbeveling om bepaalde domeinen in kaart te brengen, geeft de werkgroep per domein enkele meetinstrumenten die gebruikt zouden kunnen worden in de praktijk, zodat meer uniformiteit gerealiseerd kan worden. Bij voorkeur worden gevalideerde meetinstrumenten en vragenlijsten gebruikt.

Onderbouwing

Achtergrond

Het klinisch beeld van COVID-19 verschilt per fase (acuut/ subacuut/ herstel) en lijkt onder andere af te hangen van het premorbide niveau van functioneren. Het is belangrijk om het functioneren van patiënten die COVID-19 hebben doorgemaakt en die behandeld worden binnen de medisch specialistische revalidatie (MSR) of geriatrie revalidatiezorg (GRZ) in kaart te brengen, te volgen en te evalueren, zowel bij de start van het revalidatietraject, tussentijds als aan het einde ervan. Indien meetinstrumenten worden ingezet, dan is het belangrijk dat ze een adequaat, breed en gedetailleerd beeld van de patiënt geven.

Er is veel praktijkvariatie in welke domeinen worden gemeten, welke meetinstrumenten en vragenlijsten hiervoor worden gebruikt en wanneer deze testen worden afgenomen. In deze module worden aanbevelingen gedaan over welke domeinen in kaart gebracht moeten worden voor de evaluatie van deze patiëntengroep binnen de medisch specialistische revalidatie of geriatrie revalidatiezorg, en welke meetinstrumenten en vragenlijsten hiervoor passend zijn.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

1. What is the validity, reliability, and responsiveness of instruments used to determine and monitor the health status in patients who experienced COVID-19?
2. Which set of clinimetric instruments have been described for patients who experienced COVID-19?

P: patients who experienced COVID-19

I: set of clinimetric instrument (consisting of instruments to determine health status)

C: other set of clinimetric instruments, single instruments

O: validity, reliability, responsiveness

Relevant population

Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients admitted to the intensive care or a hospital ward other than the rehabilitation department, are excluded.

Relevant outcome measures

The working group considered validity, reliability, and responsiveness as a critical outcome measure for decision making.

The working group defined the measurement properties according to the taxonomy of the Consensus-based Standards for the selection of health Measurement INstruments (COSMIN) (Mokkink, 2010).

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1st January 2019 until 15th March 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 731 hits.

Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, including an available detailed search strategy, risk of bias assessment and an overview of the individual studies) answering the search question and meeting the additional criteria for the population and outcome measures described above. Furthermore, guidelines describing sets of clinimetric instruments were included.

None of the studies fulfilled the selection criteria, thus no studies were selected for the literature summary.

Results

No systematic reviews or relevant guidelines were found that answered the questions:

1. What is the validity, reliability, and responsiveness of instruments to determine and monitor the health status in patients who experienced COVID-19?
2. Which clinimetric-sets have been described for patients who experienced COVID-19?

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Zuurstoftherapie tijdens inspanning bij revalidatie en nazorg COVID-19

Uitgangsvraag

Wat is de waarde van zuurstofsuppletie bij desaturatie tijdens inspanning bij patiënten die COVID-19 hebben doorgemaakt en behandeld worden binnen de medisch specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ)? En wat is de plaats van het gebruik van een saturatiemeter binnen de MSR/GRZ?

Aanbeveling

Meet de perifere saturatie indien het klinisch beeld tijdens het trainen of inspanning bij dagelijkse activiteiten hiertoe aanleiding geeft (bijvoorbeeld bij dyspnoe, verhoogde ademarbeid of vermoeidheid).

Bij voldoende saturatie ($> 90\%$) of herstel binnen twee minuten

Hervat/vervolg de training, eventueel op aangepast niveau.

Bij desaturatie ($\leq 90\%$) en herstel van de saturatie duurt langer dan twee minuten

Overweeg met 1 liter zuurstof te starten (patiënten die geen zuurstof krijgen in rust) of verder te verhogen (patiënten die zuurstof krijgen in rust).

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Een gedeelte van de patiënten die vanuit het ziekenhuis of eerstelijnsverblijf worden overgeplaatst naar de medisch specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ) krijgt nog zuurstof toegediend. Het is de ervaring van de werkgroep dat de zuurstofsuppletie bij de meeste patiënten tijdens het revalidatietraject succesvol kan worden afgebouwd. Het is de vraag, zowel bij patiënten die nog extra zuurstof krijgen als bij patiënten die geen zuurstof krijgen, wat het beleid met betrekking tot het meten van de saturatie en het toedienen van (extra) zuurstof ten tijde van inspanning zou moeten zijn.

In 2020 zijn door verschillende verenigingen handvatten gepubliceerd waarin ook de monitoring en de zuurstofsuppletie bij patiënten met COVID-19 werd beschreven. Opvallend is dat het aangeraden beleid niet consistent is. Zo raadt de Vereniging voor Sportgeneeskunde (VSG) in haar Sportgeneeskundig advies (niet specifiek voor patiënten binnen de MSR of GRZ) aan om een patiënt die pre-COVID-19 niet pulmonaal belast was, een streefsaturatie van $> 92\%$ aan te houden, hieronder wordt extra zuurstof geadviseerd. Patiënten die thuis zuurstof gebruiken, kunnen dit continueren tijdens training. Het Koninklijk Nederlands Genootschap voor Fysiotherapie raadt in het standpunt 'Fysiotherapie bij Patiënten met COVID-19' (niet specifiek voor patiënten binnen de MSR of GRZ) aan om bij patiënten ten tijde van de eerste zes weken na ziekenhuisontslag de zuurstofsaturatie en hartfrequentie in rust en tijdens en na inspanning te monitoren. Als ondergrens voor het transcutaan zuurstofsaturatieniveau wordt 90% in rust en in uiterste geval 85% tijdens fysieke inspanning gehanteerd. Hiernaast wordt genoemd dat bij een saturatiedaling het belangrijk is dat de saturatie binnen twee minuten weer stijgt naar het niveau in rust. In het 'Behandeladvies Post-COVID-19 Geriatrische Revalidatie – Module Klinische revalidatie' van Verenso wordt een streefsaturatie van $\geq 92\%$ aangeraden, als grens waaronder extra zuurstof geïndiceerd is.

Deze variatie in beleid is waarschijnlijk het gevolg van het gebrek aan wetenschappelijke literatuur. Zoals blijkt uit de literatuursamenvatting zijn er geen studies gedaan naar het effect van zuurstofsuppletie bij patiënten die COVID-19 hebben doorgemaakt en desatureren tijdens inspanning. Ook over het effect van het gebruik van de saturatiemeters bij COVID-19 patiënten tijdens inspanning in de revalidatiesetting is weinig bekend.

Bij patiënten met COPD worden vaak een iets lagere saturatiewaarden geaccepteerd en wordt veelal een ondergrens van $\geq 85\%$ gesteld. Ook voor COPD-patiënten is met betrekking tot zuurstofsuppletie bij inspanning en de grenswaarde voor desaturatie, voor zover ons bekend, geen wetenschappelijke literatuur beschikbaar. De werkgroep acht de COVID-19 patiënten (uitgezonderd patiënten met onderliggend COPD) en COPD-patiënten echter niet goed vergelijkbaar. De groep patiënten met COVID-19 is meer heterogeen en heeft in tegenstelling tot COPD-patiënten geen te verwachten hypercapnie en/of chronische hypoxemie. Verder wordt bij patiënten na COVID-19 na de acute fase een verbetering in gezondheidstoestand beschreven (Van der Borst, 2020).

Het is de verwachting dat de ADL voor veel patiënten al behoorlijk inspannend kunnen zijn. Voorafgaand, tijdens en na deze activiteiten wordt de zuurstofsaturatie over het algemeen niet frequent gemeten. Er zijn de werkgroep geen casussen bekend waarbij een te lage saturatie tijdens ADL of inspanning bij COVID-19 patiënten heeft geleid tot adverse events.

De werkgroep ziet een aantal potentiële voor- en nadelen voor het gebruik van de saturatiemeter en de toediening van extra zuurstof in het geval van desaturatie bij training bij COVID-19 patiënten.

Als voordeel ligt voor de hand dat het in kaart brengen van de saturatie voor, tijdens en na de training inzicht kan geven, en indien niet afwijkend, het zowel de zorgprofessionals als de patiënt ook vertrouwen en mogelijk een gevoel van veiligheid kan geven. Aanhoudende desaturatie zou kunnen leiden tot weefselhypoxie. Bij COVID-19 patiënten zien we dat zij (zowel in de acute fase als ook in de revalidatiefase) minder goed aanvoelen wanneer zij desatureren. Bij desaturatie kunnen er maatregelen worden getroffen (onder andere zuurstofsuppletie, eerder stoppen) om de potentiële weefselhypoxie te voorkomen. Helaas is niet duidelijk bij welke duur en saturatiewaarde er schade of adverse events optreden. De werkgroep stelt arbitrair een grenswaarde van 90% tijdens het trainen of inspanning voor, indien patiënt geen klachten heeft.

Een mogelijk voordeel is dat de training effectiever zou kunnen zijn met zuurstofsuppletie. Indien desaturatie bij de patiënt de limiterende factor is tijdens de training, kan er met suppletie waarschijnlijk een hogere trainingsprikkel gegeven worden. Er is geen wetenschappelijke literatuur die dit ondersteunt, maar vanuit de inspanningsfysiologie lijkt dit effect voor de hand te liggen (Bitos, 2021).

Als laatste voordeel wordt de saturatiemeter ook vaak gebruikt om de hartfrequentie te monitoren.

Als nadelen ziet de werkgroep als eerste dat patiënten en zorgprofessionals gefixeerd zijn op de saturatiewaarden, terwijl de patiënt eigenlijk weer zou moeten leren te vertrouwen op zijn/haar lichaam. Het is onduidelijk of het meten van de saturatie voorafgaand en tijdens de training meerwaarde heeft ten opzichte van uitgaan van het klinisch beeld. Desaturatie zou zich kunnen uiten in bijvoorbeeld een hogere ademarbeid of meer dyspnoe dan verwacht op basis van de trainingsintensiteit.

Hiernaast, indien een hogere grenswaarde voor desaturatie wordt gekozen (dan fysiologisch noodzakelijk) zal de trainingsprikkel voorzichtigheidshalve gelimiteerd worden of zonder directe noodzaak zuurstof worden gegeven, waardoor de revalidatie minder optimaal of trager verloopt. Aangezien de kennis over COVID-19 nog beperkt is, is het niet onvoorstelbaar dat de huidige richtlijnen te voorzichtig zijn.

Veel instellingen gebruiken een saturatiemeter aan de vinger of teen, echter een perifere meting van de zuurstofsaturatie is niet altijd betrouwbaar en afhankelijk van de meetmethode (Nitzan, 2020). Bij factoren zoals bijvoorbeeld een verminderde perifere doorbloeding en koude acra wordt een lagere saturatiewaarde gemeten. De klinische beoordeling blijft dus erg belangrijk. Naast de sensor die op de vinger of teen van een patiënt kan worden geplaatst, zijn er ook nog sensoren die op het voorhoofd of op de neus van de patiënt geplaatst kunnen worden. Verschillende studies laten zien dat sensoren op het voorhoofd of de oorlel meer correcte resultaten gaven dan de sensoren die zuurstofsaturatie meten op de vinger van de patiënt (Jubran, 2004).

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Uit de resultaten van de patiëntenquête valt op dat weinig patiënten in deze kleine groep nog extra zuurstof krijgen ten tijde van revalidatie (van de vijftien respondenten krijgen er drie respondenten in rust zuurstof en één respondent tijdens training zuurstof), zie de bijlage 'Resultaten enquête onder patiënten'. Alle respondenten die zuurstof toegediend kregen tijdens de revalidatie, ervoeren het gebruik van zuurstof wel als ondersteunend bij de revalidatie.

Alle vijftien respondenten maakten gebruik van de saturatiemeter. Tien van de vijftien respondenten vonden dat het gebruik van de saturatiemeter bij training heeft geholpen bij de revalidatie. Er werd genoemd dat dit zorgde voor een gevoel van veiligheid, vertrouwen en rust en duidelijk maakte waar de grenzen van de patiënt lagen. Deze positieve ervaring sluit goed aan bij de positieve houding ten opzichte van het gebruik van tests en vragenlijsten.

Kosten (middelenbeslag)

Het wel of niet meten van de zuurstof brengt weinig extra kosten met zich mee. Wel dient er een saturatiemeter beschikbaar te zijn, dit is veelal het geval in de praktijk. Ook voor de (extra) zuurstofsuppletie is apparatuur of medicinale zuurstof nodig, wat mogelijk kosten met zich meebrengt. Tot zover bekend gebruiken meerdere instellingen (draagbare) concentrators. De kosten betreffen de eenmalige aanschafkosten, eventuele afschrijvingskosten, en daarna alleen de kosten van het stroomverbruik. Instellingen hebben deze apparatuur tot hun beschikking (en vaak inmiddels hun capaciteit uitgebreid), dus grote impact op kosten wordt niet meer verwacht. Er is geen informatie beschikbaar met betrekking tot de kosteneffectiviteit van de zuurstofsuppletie of saturatiemeter: het is onbekend of de potentiële baten opwegen tegen de kosten.

Aanvaardbaarheid, haalbaarheid en implementatie

Sommige zorgprofessionals zullen de voorkeur geven om, ongeacht het klinisch beeld, de saturatie te bepalen. Het veiligheidsargument speelt hierbij mogelijk een rol. Het meten van de saturatie kan de zorgprofessional het gevoel van zekerheid geven. Aan de andere kant, is het voor de zorgprofessionals ook

belangrijk om de training te optimaliseren, en zich te realiseren dat saturatiemetingen minder zekerheid geven dan het klinisch beeld, te meer daar de metingen ook beperkingen hebben.

Zuurstofbehandeling is in de revalidatiecentra beschikbaar. De concentrators en saturatiemeters werden en worden bijvoorbeeld ook voor andere doelgroepen gebruikt, of zijn inmiddels aangeschaft gedurende de COVID-19 pandemie. Ook de specifieke expertise die bij paramedici nodig is om patiënten die zuurstof krijgen bij de training te begeleiden, is over het algemeen voorhanden. De werkgroep verwacht dat het aantal FTE niet uitgebreid hoeft te worden.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Er is geen literatuur beschikbaar. De aanbevelingen moeten daarom op basis van expert opinion en het patiëntenperspectief opgesteld worden. De voor- en nadelen afwegend, komt de werkgroep tot het advies om in eerste instantie uit te gaan van het klinisch beeld. Dit betekent concreet dat patiënten die in rust hypoxemisch zijn en zuurstof krijgen met deze hoeveelheid zuurstof de training beginnen. Het voorschrijven van zuurstof betreft medisch beleid en dient daarom altijd gegeven te worden in overleg met behandelend arts en ter zake bekwaam verpleegkundig specialist of physician assistent. Voor patiënten die in rust niet hypoxemisch zijn een geen zuurstof krijgen, betekent dit dat zij zonder zuurstofsuppletie beginnen met de training of inspanning. Indien het klinisch beeld aanleiding geeft, kan de saturatie bepaald worden. Is de saturatie boven de 90% of herstelt deze binnen twee minuten naar uitgangswaarde ($> 90\%$), dan kan de training hervat worden. Is de saturatie $\leq 90\%$ en herstelt deze niet binnen twee minuten, overweeg dan zuurstofsuppletie te starten (patiënten die geen extra zuurstof krijgen in rust) of de zuurstof verder te verhogen (patiënten die zuurstof krijgen in rust). De werkgroep adviseert om te starten met één liter zuurstof en te titreren met één liter.

Onderbouwing

Achtergrond

Patiënten die opgenomen zijn geweest met COVID-19 hebben tijdens ziekenhuisopname of opname in een eerstelijnsverblijf vaak extra zuurstof nodig. Bij ontslag is dit nog niet bij alle patienten volledig gestaakt. Ook kunnen deze patiënten tijdens inspanning, zoals training of het verrichten van de activiteiten uit het dagelijks leven (ADL), nog desatureren. Fysieke training wordt soms bij (ernstige) desaturatie gestaakt of gecontinueerd met zuurstoftherapie. Het is onduidelijk wat de waarde van zuurstoftherapie is tijdens inspanning.

We zien dat er binnen de GRZ en de MSR gebruik wordt gemaakt van een saturatiemeter. De indruk bestaat dat zowel patient als hulpverlener meer waarde toekent aan de saturatiemetingen dan wenselijk of realistisch is. Verder is het onduidelijk welke consequenties de metingen zouden moeten hebben. De vraag is wat de plaats van de saturatiemeting is bij inspanning.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following questions:

1. What is the effectiveness of oxygen suppletion in the event of exercise-induced desaturation in patients post-COVID-19?

PICO1

P: patients post-COVID-19 infection

I: oxygen suppletion in the event of exercise-induced desaturation / continuation of training at low saturation

C: no oxygen suppletion in the event of exercise-induced desaturation/ stop training in the event of desaturation

O: physical functioning, adverse events (collapse, pain, dyspnea), fatigue, anxiety, patient satisfaction, physical activity, duration of rehabilitation trajectory

2. What is the value of the use of pulse oximetry during rehabilitation in post COVID-19 patients?

PICO2

P: patients post-COVID-19 infection

I: pulse oximetry usage

C: no usage of pulse oximetry

O: coping, physical functioning (for example walk test, performance test), adverse events (collapse, pain, dyspnea), fatigue, anxiety, patient satisfaction, physical activity (for example pedometer), duration of rehabilitation trajectory

Relevant populations

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients admitted to the intensive care or a hospital ward other than the rehabilitation department, are excluded.

Relevant outcome measures

PICO 1: The working group considered physical functioning and adverse events as a critical outcome measure for decision making; and fatigue, anxiety, physical activity, duration of rehabilitation trajectory and patient satisfaction as an important outcome measure for decision making.

PICO 2: The working group considered coping, physical functioning, adverse events and anxiety as a critical outcome measure for decision making; and fatigue, physical activity, duration of rehabilitation trajectory and patient satisfaction as an important outcome measure for decision making.

The working group defined the outcome measures as follows:

- Physical functioning: as determined with a validated physical performance test. Subscales of quality of life questionnaires were not included.
- Fatigue: as assessed using a validated fatigue questionnaire (for example FSS, MFIS).
- Physical activity: as determined with accelerometry or pedometry.
- Adverse events: as determined as the number of patients with at least one adverse event (for example

collapses, pain, dyspnea).

- Anxiety: as assessed using a validated anxiety questionnaire.

A priori, the working group did not define the outcome measure 'patient satisfaction', 'duration of rehabilitation trajectory' and 'coping' but used the definitions used in the studies.

The working group defined an increase of 10% of the mean or median in comparison with the baseline value of the study groups as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 31 March, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 312 hits. Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above. Two studies were initially selected based on title and abstract screening. After reading the full text, all studies were excluded because they did not fulfill the PICO criteria (see the table with reasons for exclusion under the tab Methods).

Description of studies

It was not possible to provide a summary of literature, because none of the studies fulfilled the PICO-criteria.

Conclusions

No conclusions could be drawn because of the absence of relevant comparative studies.

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Mentale en cognitieve klachten bij patiënten binnen de MSR/GRZ

Uitgangsvraag

Wat is de indicatie voor de inzet van een psycholoog in het multidisciplinaire behandelteam bij patiënten die COVID-19 hebben doorgemaakt en behandeld worden binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg? En indien een psychologische interventie geïndiceerd is, welke is dan passend en wat is de optimale timing?

Aanbeveling

Volg bij cognitieve klachten mét aantoonbaar of aannemelijk hersenletsel de richtlijn Herseninfarct en hersenbloeding. Onderstaande aanbevelingen gelden voor patiënten zonder aantoonbaar of aannemelijk hersenletsel.

Betrek een psycholoog bij de interdisciplinaire behandeling van een patiënten die COVID-19 heeft doorgemaakt indien de screeningsinstrumenten en/of de intake hier aanleiding toe geven.

Bij mentale- of cognitieve klachten

Geef erkenning voor de klachten. Start met voorlichting, adviezen en/of psycho-educatie aan patiënten en hun naasten.

Overweeg 'watchful waiting' bij milde klachten tijdens de initiële herstelfase (<3 maanden). Met screeningsinstrumenten (zie de module 'Meetinstrumenten') en handelingsobservaties kan inzicht wordt verkregen over de ernst en het beloop van de klachten.

Verwijs patiënten direct naar een psycholoog in de medisch specialistische revalidatie of geriatrische revalidatiezorg in het geval van:

- ernstige mentale klachten, coping- en/of motivatieproblemen die het behalen van de behandeldoelen belemmeren;
- aanwezigheid van psychopathologie, zoals een angst- of stemmingsstoornis; en/of
- cognitieve klachten die aanhouden ondanks adequate paramedisch behandeling of waarbij de handelingsobservaties door andere disciplines hier aanleiding toe geven.

Voor de psycholoog

Bij mentale klachten

Behandel ernstige en/of langdurige mentale klachten volgens vigerende richtlijnen.

Bij cognitieve klachten

Overweeg een neuropsychologisch onderzoek indien de cognitieve klachten persisteren na adequate behandeling en stabilisatie.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is (nog) geen wetenschappelijke evidentie beschikbaar over de effecten van screening door een psycholoog en over de effecten van psychologische behandelingen bij patiënten die COVID-19 hebben doorgemaakt. Het is echter de ervaring van de werkgroep dat er zowel bij patiënten binnen de MSR als de GRZ mentale en/of cognitieve problemen voorkomen.

Het belang van aandacht voor mentale- en cognitieve klachten bij patiënten die COVID-19 hebben doorgemaakt wordt door verschillende partijen benadrukt, zoals bijvoorbeeld in de Leidraad Nazorg voor patiënten met COVID-19 (Federatie Medisch Specialisten, 2020a) en Verenso Behandeladvies post-COVID-19 (geriatrische) revalidatie (Verenso, 2021).

Zoals eerder beschreven in de inleiding is er nog weinig bekend over de precieze impact van COVID-19 op het mentale en cognitieve functioneren. De werkgroep onderschrijft dat de gerapporteerde mentale- en cognitieve klachten niet specifiek zijn voor het doormaken van een COVID-19 infectie, maar vaker voorkomen na infecties (bijvoorbeeld Q-koorts; RIVM, 2019).

Wat betreft het mentale functioneren wijzen de eerste resultaten van onderzoek naar de prevalentie van psychopathologie bij post-COVID-19 patiënten, in de eerste fase na behandeling in het ziekenhuis, op een hoge prevalentie van PTSS, depressie, angst, slapeloosheid en obsessief-compulsieve symptomen (Mazza, 2020; Paz, 2020; Halpin, 2020; Bo, 2020; Zhang, 2020). Deze resultaten komen overeen met resultaten van eerdere studies naar de uitbraak van corona virussen waar de prevalentie van psychiatrische stoornissen varieerde tussen de 10% tot 35% (Rogers, 2020; Sheng, 2005).

De grote psychologische impact van COVID-19 kan verklaard worden door de confrontatie met een potentieel levensbedreigende ziekte, gepaard gaande met forse ademhalingsproblemen en soms snelle verslechtering, in de context van een pandemie. Hierbij kunnen onder andere sociale isolatie en een verminderd gevoel van controle en autonomie als risicofactoren gezien worden voor het ontwikkelen van psychologische problemen (Federatie Medisch Specialisten, 2020a; Federatie Medisch Specialisten, 2020b).

Wat betreft het cognitief functioneren zijn er eerste aanwijzingen dat ernstige COVID-19 infecties mogelijk kunnen leiden tot neurologische schade en verminderd cognitief functioneren (Kiekens, 2020; Stam, 2020; Simpson, 2020; Slockers, 2020). Verder is het aannemelijk dat, als we specifiek kijken naar de groep COVID-19 patiënten na een IC-opname, een deel van deze groep symptomen van het Post Intensive Care Syndroom (PICS) heeft of zal ontwikkelen.

In de praktijk valt op dat bij COVID-19 patiënten vaak uiteenlopende problematiek gezien wordt, en dat relatief veel mentale en cognitieve klachten herstellen tijdens en na het revalidatieproces (onder andere vanwege het natuurlijke beloop). Bij aanvullend onderzoek (zoals beeldvorming) kan veelal geen restschade worden aangetoond die de cognitieve klachten kunnen verklaren. Gezien de grote kans op spontaan herstel van mentale en cognitieve klachten, is het belangrijk om deze boodschap expliciet aan patiënten uit te dragen onder andere om een nocebo-effect door negatieve verwachtingen te voorkomen.

De werkgroep focust zich hier op de mentale en cognitieve klachten zonder aantoonbaar of aannemelijk

hersensletsel. Voor adviezen met betrekking tot de zorg voor post-COVID-19 patiënten mét aantoonbaar of aannemelijk hersensletsel verwijst de werkgroep naar de richtlijn Herseneninfarct en hersenbloeding (NVN, 10 2017, laatst beoordeeld 2019).

Bij sommige patiënten is de inzet van een psycholoog gewenst. In de MSR is meestal standaard een psycholoog betrokken in het multidisciplinaire revalidatieteam. Bij de GRZ ziet de werkgroep hierbij meer variatie. In sommige GRZ-teams is standaard een psycholoog betrokken, bij sommige teams niet. De werkgroep beveelt aan om, indien de screening (zie de module 'Meetinstrumenten') en intake daar aanleiding toe geven, een psycholoog standaard aan het multidisciplinaire revalidatieteam toe te voegen. Afhankelijk van de aard en ernst van de problematiek kunnen waar nodig ook andere professionals ingeschakeld worden.

Indien de patiënt mentale en/of cognitieve klachten ervaart zijn voorlichting, adviezen, psycho-educatie en/of training gericht op het versterken van de eigen veerkracht, het bevorderen van zelfmanagement en het hervinden van eigen regie belangrijke onderdelen van het revalidatieproces.

Aangezien mentale klachten frequent spontaan herstellen, is het belangrijk om in de eerste periode eerst af te wachten ('watchful waiting'). Patiënten waarbij de mentale klachten, coping- en/of motivatieproblemen het behalen van de behandeldoelen in de weg staan, dienen professioneel (bijvoorbeeld door een psycholoog) ondersteund te worden. Vanzelfsprekend dienen hierbij patiënten die psychopathologie hebben ontwikkeld, zoals een angst- of stemmingsstoornis of posttraumatische stressstoornis, zo snel mogelijk te worden verwezen naar en/of behandeld te worden door een psycholoog.

Er is tot op heden onvoldoende wetenschappelijke evidentie over de effectiviteit van specifieke (revalidatie) behandelingen voor patiënten met COVID of hun naasten. Wel is er ruime evidentie voor het effect van gerichte psychotherapeutische interventies voor patiënten met specifieke problemen, zoals Cognitieve Gedragstherapie (CGT) en *Acceptance and Commitment Therapy* (ACT) bij angst- en stemmingsklachten en Eye Movement Desensitization and Reprocessing bij posttraumatische stressklachten (EMDR) (Keijsers, 2017; Shapiro, 2018). De algemene vigerende richtlijnen voor de behandeling van mentale problemen geven een goede indicatie voor de effectiviteit van deze interventies (zie www.ggzstandaarden.nl). Bij voorkeur wordt het systeem van de patiënt betrokken bij de behandeling.

Ook bij post-COVID-19 patiënten met cognitieve klachten, zonder aantoonbaar of aannemelijk hersensletsel, is het belangrijk om spontaan herstel ('watchful waiting') af te wachten. Zolang er (lichamelijk) herstel optreedt, kan dit het cognitief functioneren beïnvloeden. Tijdens het revalidatieproces worden er screeningsinstrumenten (zie de module 'Meetinstrumenten') en handelingsobservaties ingezet waarmee de klachten in kaart worden gebracht en inzicht wordt verkregen over het beloop.

Bij ernstige interfererende cognitieve klachten kan overwogen worden om behandeling te starten met graded activity en /of cognitieve compensatie strategieën. Indien de klachten ondanks de inzet van paramedische behandeling aanhouden of de handelingsobservaties hiertoe aanleiding geven, wordt betrekken van een psycholoog aangeraden.

De werkgroep adviseert een neuropsychologisch onderzoek (NPO) te overwegen bij stabilisatie van

aanhoudende cognitieve klachten. Het is hierbij belangrijk om aandacht te hebben voor de invloed van medicatiegebruik, vermoeidheid en comorbiditeit op het cognitieve functioneren (NVKG, 2021). Te vroeg screenen met behulp van een NPO, bijvoorbeeld in de eerste weken na COVID-19, kan patiënten en naasten onnodig ongerust maken.

Indien er gekozen wordt voor 'watchful waiting' en de klachten na het revalidatietraject nog aanwezig zijn, dan kan een verwijzing naar de polikliniek Medische Psychologie/ Psychiatrie geïndiceerd zijn. Indien psychosociale problematiek meer op de voorgrond staat en er hierbij geen relatie is met de somatische problematiek, dan kan een verwijzing naar de POH-GGZ, of een psycholoog werkzaam in de generalistische basis of gespecialiseerde GGZ geïndiceerd zijn.

Waarden en voorkeuren van patiënten (en evt. hun naasten)

Mentale en cognitieve klachten worden veelal aangegeven door de patiënten zelf. Het is belangrijk dat zorgverleners hier aandacht voor hebben. Goede educatie is nodig om eventuele onzekerheden bij patiënten en hun naasten weg te nemen en om aangrijppunten te bieden voor eventuele behandeling.

Uit de patiëntenenquête bleek, dat alle respondenten (n=4) die behandeling kregen voor mentale klachten, van mening waren dat dit hielp bij hun revalidatie. Als voordelen van de behandeling van mentale- en cognitieve klachten noemden respondenten dat het aandacht krijgen voor problematiek op zich al resulteerde in een positief effect (zie de bijlage 'Resultaten enquête onder patiënten'). Twee respondenten vonden het soms emotioneel zwaar.

Patiënten gaven hiernaast aan dat ze het hebben van lotgenotencontact als waardevol ervaarden. Zorgverleners kunnen soortgelijke initiatieven stimuleren op een afdeling, door patiënten met elkaar in contact te brengen. Ook patiëntenplatforms, zoals het coronaplein.nu, kunnen hierbij helpen.

Kosten (middelenbeslag)

Er zijn geen onderzoeken gedaan naar de kosteneffectiviteit van de behandelopties voor mentale- of cognitieve klachten bij COVID-19 patiënten. Als de patiënt een indicatie heeft voor MSR of GRZ, vallen de kosten van de verschillende behandelingen meestal binnen de basisverzekering. Binnen de MSR is de psycholoog meestal betrokken. Indien bij een GRZ-afdeling de psycholoog geen standaard onderdeel uitmaakt van het revalidatieteam, dan zal dit voor de instelling extra kosten kunnen geven (bijvoorbeeld vanwege extra inzet van de psycholoog). De kosten zijn voor de werkgroep niet van (doorslaggevende) invloed geweest op de besluitvorming met betrekking tot de aanbevelingen.

Aanvaardbaarheid, haalbaarheid en implementatie

Er is in Nederland voldoende kennis en kunde bij psychologen binnen de MSR en GRZ aanwezig. Er is dus waarschijnlijk geen bijscholing nodig, wel kan het zijn dat patiënten die specifieke behandelingen behoeven, hiervoor doorverwezen moeten worden naar collega's in de generalistische basis of gespecialiseerde GGZ. Een belangrijk aandachtspunt is wel dat waar binnen de MSR de psycholoog standaard deel uitmaakt van het revalidatieteam, in de GRZ dit niet overal het geval is. De werkgroep vindt het belangrijk dat patiënten die psychologische zorg nodig hebben, deze in alle gevallen kunnen ontvangen.

Er worden verder geen problemen met betrekking tot de aanvaardbaarheid, haalbaarheid en implementatie van de huidige aanbevelingen verwacht.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Er is geen literatuur gevonden die voldoet aan de PICO. De onderstaande aanbevelingen zijn daarom grotendeels op basis van expert opinion en het patiëntperspectief tot stand gekomen.

Onderbouwing

Achtergrond

Patiënten kunnen na een COVID-19 infectie een breed scala aan klachten ontwikkelen. Over de precieze impact van COVID-19 op het mentale- en cognitieve functioneren van patiënten is nog weinig bekend. In de praktijk rapporteren veel post-COVID-19 patiënten mentale problemen (o.a. angst, depressie, posttraumatische stress, slaapproblemen), cognitieve beperkingen (o.a. concentratie of geheugenklachten, traagheid) en/of aanhoudende lichamelijke klachten (o.a. extreme vermoeidheid, uitputting, pijn). Hierbij kan sprake zijn van een complexe wisselwerking tussen bovengenoemde klachten, wat sterk pleit voor een interdisciplinaire samenwerking vanuit een biopsychosociale benadering.

Momenteel is er geen eenduidig beleid over de inzet van een psycholoog en mogelijke psychologische interventies (de psycholoog is niet overal standaard betrokken bij het interdisciplinaire behandelteam).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are beneficial and unfavourable effects of standard screening by a psychologist and, when indicated, a psychological intervention in patients who have experienced COVID-19?

P: Patients who experienced COVID-19

I: Standard screening and involvement by a psychologist and when indicated, a psychological intervention

C No standard screening

O: Quality of life, acceptance problems, mental impairments, objective and subjective cognitive impairments, and fatigue

Relevant population

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients admitted to the intensive care or a hospital ward other than the rehabilitation department, are excluded.

Relevant outcome measures

The guideline development group considered quality of life and acceptance problems as *critical* outcome measures for decision making; and mental impairments (e.g., depression, anxiety), objective and subjective cognitive impairments, and fatigue as *important* outcome measures for decision making.

A priori the working group did not define the outcome measures listed above but used the definitions used in the studies. The outcome measured should be determined using a validated instruments, questionnaires, or tests.

The working group defined an increase of 10% of the mean or median in comparison with the baseline value of the study groups as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 1st January 2019 until 3rd May 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 107 hits.

Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above. None of the studies fulfilled the selection criteria, thus no studies were selected for the literature summary.

Results

No systematic reviews were found that answered the search question.

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Slikklachten bij patiënten binnen de MSR/GRZ

Uitgangsvraag

Welke interventies worden aangeraden bij patiënten die COVID-19 hebben doorgemaakt, slikklachten hebben en behandeld worden binnen de medisch specialistische revalidatie of geriatrie revalidatiezorg?

Aanbeveling

Voor de revalidatiearts en specialist ouderengeneeskunde binnen de medische specialistische revalidatie en geriatrie revalidatiezorg

Beoordeel laagdrempelig in samenwerking met de logopedist de slikfunctie bij patiënten met een verdenking op slikklachten bij aanvang van het revalidatietraject (zie ook de module 'Meetinstrumenten').

Verwijs de patiënt bij aanwezigheid van slikklachten naar een logopedist.

Voor de logopedist

Besprek met het multidisciplinaire behandelteam welke doelen en behandelingen prioriteit hebben, en stem het behandeltraject hierop af.

Volg de vigerende richtlijn 'Orofaryngeale dysfagie'.

Bepaal of er aanpassing van de voedingsconsistenties nodig is en pas de voedingsconsistentie waar nodig in samenspraak met de diëtist aan.

Let bij de start van een behandeling op de onderstaande aspecten:

- Monitor de belastbaarheid van de patiënt tijdens de beoordeling van de slikfunctie en behandeling.
- Indien de conditie en belastbaarheid het toelaat, richt de oefeningen op slikkrachttraining, coördinatie en/of sliktempo. Houdt hierbij rekening met de aard van het slikprobleem.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er zijn geen studies gevonden waarin slikinterventies of slikadviezen zijn onderzocht bij patiënten die COVID-19 hebben doorgemaakt. Vergara (2020) bevestigt dat er beperkt wetenschappelijke artikelen op dit gebied beschikbaar zijn. Ondanks de beperkte literatuur, is de werkgroep op basis van praktijkervaring en expert opinion van mening dat slikinterventies en slikadviezen een plaats hebben bij patiënten met dysfagie, die COVID-19 hebben doorgemaakt en worden behandeld binnen de medische specialistische revalidatie (MSR) of geriatrie revalidatiezorg (GRZ). We lichten dit hieronder toe.

Dysfagie bij COVID-19 patiënten kan verschillende oorzaken hebben. Dysfagie kan bijvoorbeeld ontstaan door een neurologische aandoening, tracheotomie of intubatie (Frajkova, 2020). Wanneer men geïntubeerd is geweest kan er littekenweefsel zijn ontstaan en kunnen de spieren in het hoofd-, hals-, en keelgebied verzwakt zijn. Door activatie kunnen de spieren en daarmee de slik- en stemfunctie hersteld worden. Ook is

een veranderde sensibiliteit van de pharynxboog gezien bij patiënten met COVID-19. De werkgroep ervaart in de praktijk dat dysfagie bij COVID-19 patiënten veelal samenhangt met de beperkte conditie en vermoeidheid. Binnen de GRZ revalideren ook ouderen met presbyfagie, naast het feit dat zij COVID-19 hebben doorgemaakt. Presbyfagie is een functionele maar kwetsbaardere slikfunctie door het natuurlijke verouderingsproces (Azzolino, 2019). In het geval van ziekte zoals COVID-19, heeft de oudere patiënt met presbyfagie een groter risico op een slikstoornis. Fysiologische veranderingen (zoals bijvoorbeeld spiermassaverlies, minder soepele weefsels, verminderde speekselproductie, een slechter gebit, verminderde gevoeligheid in mond- of keelgebied, afname van reuk- en smaakfuncties) bij het ouder worden kunnen het risico op dysfagie verhogen.

Het is belangrijk dat bij aanvang van het revalidatietraject stilgestaan wordt bij dysfagie. In sommige gevallen zal in het ziekenhuis al gescreend zijn op slikklachten, voordat patiënten zorg ontvangen binnen de MSR of GRZ. Indien dysfagie eerder is gesignaleerd of gesignaleerd wordt in de MSR of GRZ (zie ook de module 'Meetinstrumenten'), verwijs patiënten dan naar een logopedist.

Wanneer slikobservaties en het klinisch oordeel van de logopedist maken dat er twijfel bestaat over de slikfunctie of het slikprobleem, kan er objectiever onderzoek worden aangevraagd. Verschillende onderzoeken zijn beschikbaar:

Video Fluoroscopische Evaluatie van het Slikken (VFES)

Dit betreft het klassieke referentieonderzoek voor de diagnose dysfagie (Nawaz, 2018; NVKNO 2017), waarbij een video-opname van het slikproces wordt gemaakt. De resultaten van dit onderzoek geven een duidelijker beeld van de verschillende behandelingsmogelijkheden.

Flexibele Endoscopische Evaluatie van het Slikken (FEES)

Dit betreft een onderzoek dat de anatomie en de dynamiek van het slikken beoordeelt (Nawaz, 2018; NVKNO, 2017). Dit onderzoek vereist geen radiologische uitrusting; het kan langer duren dan het radiologische onderzoek, maar er kunnen meer tests met voedsel van verschillende consistentie worden uitgevoerd.

Deze technische en meer invasieve onderzoeken geven een objectiever oordeel over de aard en ernst van dysfagie (Baijens, 2016). De werkgroep adviseert om bij indicatie voor onderzoek, in overleg met patiënt en waar nodig in overleg met de KNO-arts of radioloog, en afgestemd op de belastbaarheid, een slikonderzoek met behulp van een VFES of FEES te verrichten. Per patiënt dient te worden afgewogen welk onderzoek gewenst is. Mocht er binnen een zorginstelling geen VFES of FEES beschikbaar zijn, dan is laagdrempelige afstemming en goede communicatie tussen zorgprofessionals en zorginstellingen gewenst (zie de module 'Overleg- en doorverwijsmogelijkheden').

Als patiënten last hebben van dysfagie, dient onderzocht te worden wat de beste aanpak voor deze klachten kan zijn. Het kan zijn dat bij patiënten de klachten al herstellen met de verbetering van de conditie. In andere gevallen kan het de voorkeur hebben om een behandeling te starten. In de Richtlijn Orofaryngeale Dysfagie (NVKNO, 2017) staat beschreven dat dysfagie op twee manieren behandeld kan worden: compensatiestrategie of sliktraining. Bij ernstige COVID-19 klachten, waar veiligheid of voldoende intake in gedrang komt, kan de behandeling eerst gericht worden op compensatie.

Een compensatiestrategie betreft het consequent toepassen van specifieke aanpassingen.

Compensatiestrategieën kunnen zijn het wijzigen van de houding van de patiënt, het aanpassen van de positie van het hoofd tijdens slikken en/of op een andere manier slikken. Ook het wijzigen van de consistentie van het eten of drinken is een compensatiestrategie. Denk bijvoorbeeld aan het verdikken van dun-vloeibare dranken, fijn of dik-vloeibaar maken van vast voedsel. Om voeding consequent aan te passen en inzichtelijk te maken, kan de International Dysphagia Diet Standardization Initiative (IDDSI) gebruikt worden (Cichero, 2016; Su, 2018). Dit internationale raamwerk kan gebruikt worden om verschillende consistenties van eten en drinken in te delen. Het afstemmen en aanpassen van consistenties dient in overleg te gebeuren met de diëtist. Hierbij moet worden afgewogen welke consistentie en welke hoeveelheden veilig zijn en wat mogelijk is in combinatie met eventuele zuurstoftherapie of sondevoeding. Wanneer men het eten en drinken oefent, maar het niet lukt om aan voldoende intake te komen dan is het moeilijker om een optimale conditie te behouden en daarmee een veilige slikfunctie.

Sliktraining kan worden geïndiceerd bij dysfagie waarbij functieherstel te verwachten is. Afhankelijk van de aard van dysfagie, kan sliktraining zich richten op slikkracht, coördinatie of sliktempo, waarbij met oefeningen gericht op het verbeteren van de slikkracht ook indirect de coördinatie en het sliktempo wordt verbeterd. Als de patiënt bijvoorbeeld vast voedsel moeilijk kan slikken is het zinvol oefeningen te richten op slikkracht. Echter, als de patiënt zich wisselend verslikt in dunne dranken is het sliktempo een belangrijk punt van aandacht tijdens de oefeningen. Indien de belastbaarheid en de conditie van de patiënt het toestaat, kan ook sliktraining met manoeuvres (bijvoorbeeld de Mendelsohn manoeuvre) een optie zijn. Bij de Mendelsohn manoeuvre spant de patiënt langdurig mondbodemspieren aan (McCullough, 2012; Ashford, 2009). Het is van belang om de intensiteit en frequentie van de sliktraining af te stemmen op de conditie en belastbaarheid van de patiënt.

Het is belangrijk dat de exacte interventie door de logopedist, diëtist en binnen het multidisciplinaire behandelteam wordt afgestemd. Er kan prioriteit aan bepaalde behandeldoelen worden gegeven. Daarnaast is het bijvoorbeeld van belang om in het behandelteam te bespreken of een patiënt het conditioneel aankan om over te stappen naar normale voedingsconsistenties en of een voedingssonde verwijderd kan worden (zie ook module 'Voedingsinterventies').

Tijdens de maaltijdmomenten en behandelingen dient de belastbaarheid gemonitord te worden. De werkgroep ervaart in de praktijk dat de belastbaarheid van een patiënt die COVID-19 heeft doorgemaakt een wisselend beeld kan geven gedurende de dag. Iemand kan bijvoorbeeld het ontbijt goed uitgerust nuttigen, maar na de therapiesessies in de ochtend volledig uitgeput en benauwd zijn. Het is belangrijk aandacht te hebben voor het feit dat de dagelijkse activiteiten ook inspannende activiteiten zijn en evenzeer een onderdeel zijn van de revalidatie. Daarnaast kan bijvoorbeeld ook een goede mondverzorging bijdrage aan de behandeling. Een slechte mondgezondheid kan eerder aanleiding geven tot een pneumonie bij aspiratie (Warren, 2019).

Het behandelen van COVID-19 patiënten met dysfagie is dus een dynamisch proces, waarbij de interventie en de monitoring (evaluatie van behandeling) nauw met elkaar verbonden en complementair zijn. Nauwkeurige monitoring is bij deze patiëntengroep van groot belang. In de module 'Meetinstrumenten' worden

verschillende screenings- en slikonderzoeken omschreven.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Patiënten willen veelal weer kunnen eten en aan hun herstel werken. Enkele patiënten ervaren angst om de slikfunctie te versterken. Daarnaast kiezen enkele patiënten er ook geregeld voor om, ondanks dat het slikken veilig is, het eten en drinken nog niet uit te breiden omdat het te veel energie kost. Het veilig eten en drinken wordt dan als te vermoeiend ervaren.

Kosten (middelenbeslag)

Er is geen informatie over de kosteneffectiviteit bekend. Met betrekking tot producten zullen de kosten van de aanbevelingen meevallen en geen grote impact op de totale zorgkosten hebben. Er zullen wel kosten worden gemaakt voor behandeluren, maar dit is niet specifiek voor deze patiëntengroep.

Aanvaardbaarheid, haalbaarheid en implementatie

Samenwerking tussen verschillende disciplines is cruciaal, waarbij een goede overdracht essentieel is. Logopedisten moeten betrokken zijn in het revalidatietraject als er een logopedische hulpvraag is. Als voorwaarde geldt dat er voldoende formatie aan logopedisten moet zijn binnen een zorginstelling. Hoewel er wat praktijkvariatie zal zijn, is de verwachting dat dit in de meeste MSR en GRZ-instellingen in de huidige situatie geregeld is.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Hoewel er nog weinig evidentie is voor slikinterventies bij patiënten die COVID-19 hebben doorgemaakt, is de werkgroep wel van mening dat aandacht voor slikklachten, middels het laagdrempelig beoordelen van de slikfunctie, slikinterventies en/of slikadviezen een belangrijk onderdeel uitmaakt van een geriatrische of medisch specialistisch revalidatiebehandeling. De richtlijn Orofaryngeale dysfagie biedt goede handvatten. Een goede vocht- en voedingsinname en effectieve behandeling van slikstoornissen ondersteunen het herstelproces.

Onderbouwing

Achtergrond

Dysfagie is een verzamelnaam voor slikklachten of slikstoornissen. Dysfagie kan het gevolg zijn van een lage belastbaarheid, een beperkte conditie of afwijkingen in de aansturing van de slikbeweging in de verschillende fases bij patiënten met Covid-19. Tekenen van dysfagie zijn onder andere verslikken, hoesten, kokhalzen, betraande ogen tijdens eten/drinken, veranderende stemkwaliteit na eten/drinken, vermijden van bepaalde voedingsmiddelen of onbedoeld gewichtsverlies. Dysfagie vormt een belangrijke risicofactor voor problemen als ondervoeding, uitdroging of longontsteking (Gallegos, 2016; Okazaki, 2019; Ortega, 2017). Slikproblematiek wordt relatief vaak gezien bij COVID-19 patiënten, maar de oorzaak varieert tussen patiënten (bijvoorbeeld als gevolg van intubatie, fysieke aandoening, slechte conditie, neurologische aandoeningen) (Frajkova, 2020). Vanwege verschillende oorzaken van slikproblematiek is de optimale behandeling naar verwachting variërend voor de individuele COVID-19 patiënt binnen de medisch specialistische revalidatie (MSR) of geriatrische revalidatiezorg (GRZ).

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:
What are the beneficial and unfavourable effects of specific swallowing interventions in patients with dysphagia after SARS-COV-2 infection?

P: patients with dysphagia after SARS-COV-2 infection

I: a specific intervention, advice, instructions related to swallowing

C: usual care/ other types of interventions

O: swallowing function, strength (swallow, chew, cough), dyspnea, swallow speed, swallow anxiety, functional oral intake (i.e. oral or tube feeding), nutritional intake (portion size, eating speed)

Relevant populations

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients during the acute phase who received the intervention in the intensive care or a hospital ward, are excluded.

Relevant outcome measures

The working group considered swallowing function and strength (swallow, chew, cough) as a critical outcome measure for decision making; and dyspnea, swallow speed, swallow anxiety, functional oral intake (oral or tube feeding), and nutritional intake (portion size, eating speed) as an important outcome measure for decision making.

The working group defined the outcome measures as follows:

- Swallowing function: as determined with direct observation or validated swallow tests (for example water swallow test, 'intra-oraal onderzoek', Volume- Viscosity Swallowing Test, bolus swallow test, 'flexible endoscopic evaluation of swallowing', 'videofluoroscopic swallowing study').
- Strength (swallow, chew, cough): as determined with a validated test (e.g. tongue force measurement, SilverFit Rephagia).
- Dyspnea: as determined using a validated instrument, assessed at rest, during exercise, and/or during speech.
- Swallow speed: as determined with direct observation or using a validated instrument (for example maximum swallowing rate).
- Swallow anxiety: using validated questionnaires (e.g. Dysphagia Handicap Index).
- Functional oral intake (oral or tube feeding): as determined with a validated questionnaire (for example: Functional Oral Intake Scale).
- Nutritional intake (portion size, eating speed): as determined with validated questionnaires (for example 24h recall, food diary).

The working group defined an increase of 10% of the mean or median in comparison with the baseline value of the study groups as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 7 June, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 152 hits. Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above. None of the studies fulfilled the selection criteria, thus no studies were selected for the literature summary.

Results

No systematic reviews were found that answered the search question. Some descriptive studies, however, were found that mentioned relevant points of attention in swallowing interventions in COVID-19, these studies are addressed in 'overwegingen'.

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Voedingsinterventies binnen de MSR/GRZ

Uitgangsvraag

Welke voedingsinterventie kunnen we aanbevelen bij patiënten die opgenomen zijn geweest in het ziekenhuis of eerstelijnsverblijf met COVID-19 en behandeld worden binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg?

Aanbeveling

Meet en monitor de voedingstoestand, lichaamssamenstelling en het gewicht van de patiënt (zie ook de module 'Meetinstrumenten').

Schrijf op basis van de gemeten spiermassa en gewichtsverloop een energierijk- en eiwitrijkdieet met voldoende vocht voor. Maak waar nodig gebruik van een supplement, medische drink- en/of sondevoeding.

- Bij ondergewicht of normaal gewicht richt de interventie op toename of behoud van gewicht en opbouw van spiermassa;
- Bij overgewicht richt de interventie initieel op het stabiliseren van het gewicht en opbouw van spiermassa en eventueel in een later stadium op gewichtsnormalisatie.

Pas de voedingsinterventies aan op de individuele problematiek van de patiënt. Houd in het bijzonder rekening met vermoeidheid, vaak lage belastbaarheid en geur en/of smaakverandering.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Het doel van deze uitgangsvraag was om te achterhalen welke voedingsinterventies aanbevolen kunnen worden bij patiënten die opgenomen zijn geweest in het ziekenhuis of eerstelijnsverblijf met COVID-19 en behandeld worden binnen de medisch specialistische revalidatie of geriatrische revalidatiezorg. Er zijn geen systematische reviews, RCT's of andere relevante studies gevonden gericht op voedingsinterventies in deze studiepopulatie. Hier ligt een kennislacune.

Door verschillende partijen is reeds wel het belang van een goede voedingsstatus bij patiënten met COVID-19 benadrukt. In de Leidraad Nazorg voor patiënten met COVID-19 wordt de noodzaak voor een goede voedingsstatus onderschreven (Federatie Medisch Specialisten, 2020). Ook Verenso (2020) adresseert het verbeteren voedingstoestand en goede intake als een van de behandeldoelen van (geriatrische) revalidatie (Verenso Behandeladvies post-COVID-19 (geriatrische) revalidatie). Een prospectieve éénarmige observationele studie (Hoyois, 2021) die door gebrek aan een controleconditie niet kon worden opgenomen in de literatuursamenvatting, onderzocht medische voedingstherapie (conform ESPEN criteria; Barazzoni, 2020) bij kritieke COVID-19-patiënten na IC opname. Hoyois (2021) concludeerde dat de gestandaardiseerde medische voedingstherapie en intensieve fysieke revalidatie tot een verbetering van de voedingsparameters leiden bij post-IC-COVID-19 patiënten met ondervoeding en een lage spiermassa. Hoewel dit een andere setting betreft en de generaliseerbaarheid onduidelijk is, is de verwachting dat hierin overeenkomsten kunnen zitten voor de doelpopulatie van deze richtlijn. De Nederlandse COVOED studie (Wierdsma, 2021) uitgevoerd

onder 407 COVID-19 patiënten, laat zien dat verminderde eetlust, vol gevoel, benauwdheid, veranderde smaak en verlies van smaak de meest genoemde klachten zijn na ontslag uit het ziekenhuis. Deze factoren zijn allen van invloed op de voedingstoestand.

Indien de voedingstoestand en lichaamssamenstelling bij opname in de MSR of GRZ nog niet in kaart zijn gebracht, kan op ondervoeding gescreend worden met bijvoorbeeld de SNAQ65+ en MNA (of MNA-SF). De lichaamssamenstelling (vetvrije massa) kan gemeten worden met een bio-impedantiemeter (NAP, 2021) (zie ook module 'Meetinstrumenten'). Tevens is het belangrijk de voedingsinname in kaart te brengen. Bij aanwezigheid van voeding gerelateerde klachten, pleit de werkgroep voor het voorschrijven van een energierijk en eiwitrijk dieet met voldoende vocht, al dan niet met een supplement, aangepaste consistentie, medische drinkvoeding en/of sondevoeding. Adviezen conform de ESPEN-criteria (Barazzoni, 2020), de richtlijn 'Ondervoeding' (Kruizenga, 2019) en de richtlijn 'Ondervoeding bij de geriatrische patiënt' (NVKG, 2013) kunnen hiervoor basis bieden. Hieronder lichten we dit verder toe.

Bij COVID-19 patiënten in de MSR of GRZ is veelal vanwege longfunctieproblematiek, verminderde conditie, lage belastbaarheid of afgenomen gewicht/spiermassa (gewijzigde lichaamssamenstelling) de behoefte aan energie en eiwitten verhoogd. In de beginfase van MSR of GRZ is bij vrijwel alle patiënten een voedingsinterventie belangrijk om voldoende energie- en eiwitinname te waarborgen. Bij patiënten met ondergewicht of een normaal gewicht is het doel van de interventie toename of behoud van gewicht én toename van spiermassa. Bij patiënten met overgewicht is het primaire doel van de interventie initieel het stabiliseren van het gewicht én toename van spiermassa.

Goede energie-inname is essentieel om te voorzien in de verhoogde behoefte qua herstel en gewichtsbehoud. Een eiwitverrijkt voedingspatroon in combinatie met beweging zorgt voor opbouw van spiermassa en preventie van verlies van spiermassa bij ziekte, slechte voedingsinname en inactiviteit. Om voldoende energie- en eiwitinname te realiseren kan gebruik gemaakt te worden van eiwit-supplementen en medische drink- en sondevoeding. De werkgroep adviseert vigerende richtlijnen te volgen voor specifieke hoeveelheden qua energie- en eiwitinname (Barazzoni, 2020; Kruizenga, 2019; NVKG, 2013). De lichaamssamenstelling kan gemeten worden met een bio-impedantie meter (NAP, 2021), om vervolgens met de berekende spiermassa de individuele eiwitbehoefte te bepalen. Indien het uitvoeren van bio-impedantie meting niet mogelijk is (bijvoorbeeld vanwege geen beschikbare apparatuur of hygiëneregels bij patiënt in besmettelijke fase) kan als alternatief de formule van Gallagher gebruikt worden om de vetvrijemassa te bepalen (Gallagher, 2000; zie ook module 'meetinstrumenten'). Gedurende het revalidatietraject dient de voedingsinname afgestemd te worden op de behandeldoelen van de patiënt. Bijvoorbeeld: pas de consistentie aan bij verbetering van de slikfunctie, of bouw de sondevoeding af indien de orale intake uitbreidt.

In het tweede deel van de klinische revalidatie verschuift de inzet van een energie- en eiwitrijke voedingsinterventie naar een eiwitrijke voedingsinterventie. Voor het monitoren van het effect van de voedingsinterventie wordt bij voorkeur verandering in lichaamssamenstelling en het gewichtsverloop gemeten.

Naast de verminderde voedingsstatus en de lage belastbaarheid bij de start van het revalidatietraject, hebben veel patiënten één of meer aan voeding gerelateerde klachten. Deze klachten kunnen ook leiden tot een verminderde voedingsstatus.

Veel voorkomende klachten zijn een vol gevoel, benauwdheid en vermoeidheid, verlies of verandering van smaak en/of reukvermogen, droge mond en spierzwakte (armfunctie, slikkracht, kauwspieren). Vooral de benauwdheid en vermoeidheid, geur- en smaakverandering/verlies en slikstoornissen op basis van zwakte lijken specifiek voor de patiënt die COVID-19 heeft doorgebracht. Hieronder lichten we deze klachten toe:

Benauwdheid en vermoeidheid

Specifiek bij COVID-19 zal bij het aanbieden van de voeding bij de patiënt rekening gehouden moeten worden met de benauwdheid en vermoeidheid. Hierbij kan gedacht worden aan aanbod van vloeibare, smeuge, zachte en eventueel gemalen voeding in kleine porties met een hoge voedingswaarde.

Geur- en smaakverandering/verlies

Verandering, afname of verlies van smaak heeft een duidelijk effect op eetplezier en beleving van een maaltijd. Om de voedingsinname van de patiënt toch zo optimaal mogelijk te krijgen, is het van belang rekening te houden met 'aversie tegen bepaalde smaken en geuren' en deze waar mogelijk te vermijden en te vervangen door producten die de patiënt wel kan verdragen. Verder kan er gewerkt worden met stimuleren van geur- en/of smaakbeleving (zie Alliantie Voeding in de Zorg, 2020).

Slikstoornissen

Bij slikstoornissen krijgt de patiënt sondevoeding of wordt voeding aangeboden in een consistentie die veilig is voor de patiënt om te kauwen/slikken (zie ook module 'Slikklachten'). De diëtist bekijkt met de patiënt welke hoeveelheden binnen de geadviseerde consistentie (*International Dysphagia Diet Standardization Initiative*; Cichero, 2017) nodig zijn voor voldoende vocht- en voedingsinname. De logopedist en diëtist stemmen onderling haalbaarheid en hoeveelheden af. Daarnaast kiezen enkele patiënten er ook voor om, ondanks dat het slikken veilig is, het eten en drinken nog niet uit te breiden omdat het te veel energie kost. Het veilig eten en drinken wordt dan als te vermoeiend ervaren. De patiënt kiest er dan bijvoorbeeld langer voor om de korst van het brood te halen en smeuge/zachte voeding te gebruiken.

In geval van co-morbiditeit, hou in de behandeling rekening met vigerende dieetadviezen en richtlijnen (bijvoorbeeld [Richtlijn CVRM](#) (NHG, NIV en NVvC, 2019); [Richtlijn Diabetes Mellitus](#) (NIV, 2018), NHG standaard COPD, [Chronische nierschade](#) (NHG en NIV, 2018), [dieetbehandelingsrichtlijnen.nl](#), [voedingskennis.nl](#))

De verhoogde eiwitbehoefte houdt ook na het ontslag uit MSR/GRZ aan (van Zanten, 2019). Naast de genoemde voedingsinterventies is het belangrijk om al tijdens het revalidatietraject met de patiënt aandacht te hebben voor een gezonde leefstijl: motiveer patiënten om ook na afloop van het revalidatietraject een actieve (naar mogelijkheden) en gezonde levensstijl aan te houden. Bij sommige patiënten kan een overdracht naar een diëtist in de eerste lijn nodig zijn.

Waarden en voorkeuren van patiënten (en eventueel hun verzorgers)

Voor patiënten is het belangrijk om zelfstandig eten en drinken naar wens te kunnen nuttigen. Zij kunnen de

afhankelijkheid van medische drink- en/of sondevoeding aan de start van de MSR of GRZ als onprettig ervaren. De lage belastbaarheid en het lage eettempo in combinatie met vele uitdagingen op fysiek vlak, maakt dat elke activiteit rondom eten en drinken als belastend kan worden ervaren. Medische drink- en sondevoeding werken ondersteunend, zodat er meer energie overblijft voor (fysieke) therapie. Patiënten hechten aan goede uitleg en informatie over medische drink- en sondevoeding. Minder druk op eten en drinken ('minder moeten') lijkt in praktijk gewaardeerd te worden. Sommige patiënten vinden ook energie- en/of eiwit verrijkte extraatjes prettiger/smaakvoller dan medische drinkvoeding. Naarmate het fysiek herstel vordert wordt vaak ook een verbetering in reguliere voedingsinname gezien, waarbij ook eigen regievoering meer centraal komt.

Gewichtsverlies tijdens ziekenhuisopname wordt voor patiënten met overgewicht vaak gezien als prettige bijkomstigheid. Echter, het nadelige effect dat dit vooral verlies van spiermassa is wordt hierbij niet altijd ingezien. De patiënt is niet altijd bekend met het positieve effect van voldoende energie- en eiwitinname op het herstel.

Kosten (middelenbeslag)

Voedingsinterventies hebben een vaste rol binnen de klinische MSR of GRZ en worden dusdanig gedekt uit de daartoe bestemde DBC's. Het gebruik van medische drink- en sondevoeding ligt in deze patiëntenpopulatie naar verwachting wel hoger dan bij de reguliere revalidatiepopulaties. Bij ambulante/poliklinische MSR of GRZ-patiënten wordt medische drink- of sondevoeding vergoed door de zorgverzekeraar.

Aanvaardbaarheid, haalbaarheid en implementatie

Voedingsinterventies specifiek voor COVID-19 patiënten binnen MSR of GRZ zijn vergelijkbaar met andere patiënten populaties. De benodigde (medische) voedingsproducten zijn veelal standaard aanwezig binnen de zorginstellingen. Bij deze patiëntengroep is inzet van de diëtist nodig en tevens ondersteuning (begeleiden bij eten en drinken) door verpleging/verzorging. Er zijn verder geen aspecten op het gebied van de aanvaardbaarheid, haalbaarheid en implementatie die van invloed zijn op de besluitvorming.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Hoewel er geen evidence beschikbaar is voor een voedingsinterventie bij patiënten na doorgemaakte COVID-19 infectie, is de werkgroep van mening dat voedingsinterventie bij de meeste patiënten noodzakelijk is. De voedingsinterventie richt zich op het verbeteren dan wel optimaliseren van de voedingstoestand van de patiënt, wat een voorwaarde is voor het fysieke herstel van de patiënt.

Onderbouwing

Achtergrond

Lage belastbaarheid in combinatie met ziekte gerelateerde ondervoeding (cachexie en sarcopenie), eventuele co-morbiditeit, en vaak voorkomende aanwezigheid van onder andere verminderde eetlust, vermoeidheid, slikproblematiek, veranderde en verminderde smaak en gastro-intestinale problemen maken dat aandacht voor adequate en/of aangepaste voedingsinname bij patiënten die COVID-19 hebben doorgemaakt essentieel is. Een adequate voedingsinname kan in zijn algemeenheid resulteren in verbeterde

functionaliteit, een lager risico op complicaties en een kortere herstelperiode. De voedingstoestand van patiënten die COVID-19 hebben doorgemaakt kan mogelijk ook verbeterd worden door voedingsinterventies en begeleiding.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What is the effectiveness of (specific) nutritional interventions in comparison to usual care in patients who have experienced COVID-19?

P: patients who have experienced COVID-19

I: (specific) nutritional interventions

C: placebo/ usual care

O: body composition, physical functioning, quality of life, tube feeding, medical nutrition, fatigue, duration of the rehabilitation trajectory

Relevant populations

Only studies with ≥ 20 (ten in each study arm) adult COVID-19 patients were included. Patients with COVID-19 were eligible regardless of the time since active viral infection and the severity of the disease. However, patients during the acute phase who received the intervention in the intensive care or a hospital ward, are excluded.

Relevant outcome measures

The working group considered lean body mass, physical functioning, and quality of life as a critical outcome measure for decision making; and tube feeding, medical nutrition, fatigue, duration of the rehabilitation trajectory as an important outcome measure for decision making.

The working group defined the outcome measures as follows:

- Body composition: as determined with a DEXA-scan or a validated bio-electrical impedance analyser (fat mass and fat free mass).
- Physical functioning: as determined with a validated physical performance test or validated questionnaires.
- Quality of life: as determined with a validated quality of life questionnaire (for example 36-item Short Form Health Survey, EuroQol-5D).
- Fatigue: as determined with a validated fatigue questionnaire (for example the Fatigue Severity Scale, Modified Fatigue Impact Scale)

The working group did not define the outcomes tube feeding, medical nutrition and duration of the rehabilitation trajectory, but used the definitions used in the included studies.

For all outcomes, the working group defined an increase of 10% of the mean or median in comparison with the baseline value of the study groups as a minimal clinically (patient) important difference.

Search and select (Methods)

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms until 19 May, 2021. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 1,463 hits. Studies were selected based on the following criteria: systematic reviews (searched in at least two databases, and detailed search strategy, risk of bias assessment and results of individual studies available), randomized controlled trials and comparative observational studies answering the search question and meeting the additional criteria for the population and outcome measures described above. No studies were selected based on title and abstract screening, because they did not fulfill the PICO criteria.

Description of studies

It was not possible to provide a summary of literature, because none of the studies fulfilled the PICO-criteria.

Results

No conclusions could be drawn because of the absence of relevant comparative studies.

Verantwoording

Laatst beoordeeld : 14-01-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Overleg- en doorverwijsmogelijkheden na COVID-19

Uitgangsvraag

Welke externe consultatiemogelijkheden dienen beschikbaar te zijn om adequate medisch specialistische revalidatiezorg of geriatrische revalidatiezorg te kunnen leveren aan patiënten die COVID-19 hebben doorgemaakt?

Aanbeveling

Voor revalidatieartsen binnen de medisch specialistische revalidatie (MSR) en specialisten ouderengeneeskunde binnen de geriatrische revalidatiezorg (GRZ)

- Consulteer een orgaanspecialist in het geval van nieuwe of blijvende klachten die de revalidatiebehandeling vertragen en kunnen duiden op mogelijke orgaanschade.
- Consulteer een psychiater, medisch psycholoog of GZ-psycholoog in geval van post-traumatische stress, cognitieve beperkingen of mentale klachten na (IC) opname. Overweeg consultatie voor nadere diagnostiek en/of behandeling in het geval van aanhoudende lichamelijke klachten waarbij de patiënt niet of onvoldoende profiteert van het geboden multidisciplinaire revalidatietraject.
- Consulteer een klinisch geriater, internist ouderengeneeskunde of specialist ouderen geneeskunde in het geval van problematiek met betrekking tot geriatrische aspecten zoals *frailty*, sarcopenie, polyfarmacie of andere geriatrische syndromen.
- Consulteer een geestelijk verzorger bij levensvragen/-problematiek.

Voor revalidatieartsen binnen de MSR

- Consulteer een sportarts of fysiotherapeut met aandachtsgebied inspanningsfysiologie in het geval van aanwijzingen van aanhoudende inspanningsintolerantie.
- Consulteer een specialist ouderengeneeskunde (kaderarts GRZ) in het geval van comorbiditeit en complexere zorgvraag.

Voor specialisten ouderengeneeskunde binnen de GRZ

- Consulteer een revalidatiearts in het geval van complexere revalidatiedoelen, mogelijke indicatie voor MSR en complexe musculoskeletale complicaties.

Overwegingen

Kenmerkend voor de groep patiënten die revalideert na een ziekenhuisopname bij COVID-19, zijn klachten van forse deconditionering vaak in combinatie met klachten die passen bij status na langdurige immobilisatie. Daarnaast is er frequent sprake van zuurstofafhankelijkheid (Federatie Medisch Specialisten, 2021). Doordat COVID-19 een nieuwe ziekte is en gezien de grote variatie in het herstel- en klachtenpatroon, is voor veel zorgverleners lastig in te schatten welke klachten aanvullende aandacht vereisen. Soms blijkt de eerste indicatiestelling suboptimaal. Afhankelijk van de problematiek is het daarom belangrijk om naast de

zorgverleners uit het revalidatieteam, ook andere (medisch) specialisten bij het (poli)klinische revalidatietraject te kunnen betrekken. Dit moet tijdig gebeuren, zodat het revalidatietraject niet onnodig wordt vertraagd en er eventueel tijdig diagnostiek en behandeling kan plaatsvinden. Het is daarom aan te raden dat een aantal standaard overleg- en/of doorverwijsmogelijkheden op afroep aanwezig zijn en dat indien nodig van deze mogelijkheden gebruik wordt gemaakt (dat wil zeggen: dat de patiënt bijvoorbeeld wordt doorverwezen, of dat een consulent gevraagd wordt om een MDO bij te wonen). Hierbij moet gedacht worden aan de volgende zorgprofessionals:

- Een orgaanspecialist in het geval van nieuwe of blijvende klachten die de revalidatiebehandeling vertragen en kunnen duiden op mogelijke orgaanschade (bijvoorbeeld een longarts of cardioloog).
- Een expert op het vlak van de klinische inspanningsfysiologie (bijvoorbeeld een sportarts of fysiotherapeut met aandachtsgebied inspanningsfysiologie).
- Een revalidatiearts bij patiënten binnen de geriatrische revalidatiezorg (GRZ) voor patiënten waarbij er bijvoorbeeld sprake is van complexere revalidatiedoelen, mogelijke indicatie voor medisch specialistische revalidatie (MSR), complexe musculoskeletale complicaties of functieverlies waarvoor indicatie orthesen.
- Een specialist ouderengeneeskunde bij patiënten binnen de MSR in het geval van kwetsbare patiënten, in de context van comorbiditeit en complexe zorgvraag.
- Een klinisch geriater, internist ouderengeneeskunde of specialist ouderengeneeskunde in het geval van problematiek met betrekking tot geriatrische aspecten zoals *frailty*, cognitieve beperkingen sarcopenie, polyfarmacie of andere geriatrische syndromen.
- Een psychiater, medisch psycholoog of GZ-psycholoog in geval van post-traumatische stress, cognitieve beperkingen of mentale klachten na (IC) opname of voor nadere diagnostiek en/of behandeling in het geval van aanhoudende lichamelijke klachten waarbij de patiënt niet of onvoldoende profiteert van het geboden multidisciplinaire revalidatietraject.
- Een geestelijk verzorger bij levensvragen/-problematiek.

Kosten

Overleg tussen zorgprofessionals wordt veelal niet vergoed. Echter, deze kosten zouden intercollegiaal overleg niet in de weg mogen staan. Veel instellingen die GRZ aanbieden hebben reeds afspraken omtrent consulentschap door de revalidatiearts. Expertise op het vlak van inspanningsfysiologie is in veel MSR instellingen reeds aanwezig, of reeds beschikbaar via bestaande samenwerkingen met bijvoorbeeld ziekenhuizen.

Implementatie, haalbaarheid en aanvaardbaarheid

Bij patiënten met COVID-19 blijkt vaker dan bij veel andere aandoeningen afstemming met professionals buiten het revalidatieteam noodzakelijk. De druk op het zorgsysteem door de COVID-19 pandemie heeft als gevolg dat op sommige plekken de wachttijden toenemen. De werkgroep vermoedt dat er momenteel te weinig consultatie of doorverwijzingen plaatsvinden door de capaciteitsproblemen, deels reeds bestaande voor en toegenomen door de COVID-19 pandemie. Echter, gezien het belang voor de patiënt is het belangrijk dat deze drempels overwonnen worden.

De afstemming vraagt verder om goede communicatie binnen het lokale zorgnetwerk en goede afspraken

over onderlinge consultatie en rolverdeling. De onderlinge afstemming tussen de MSR- en GRZ-instellingen is in sommige regio's ook een ontwikkelpunt. Hier is aandacht voor nodig. De werkgroep verwacht niet dat er verder onoverkomelijke problemen zullen zijn met betrekking tot de implementatie en haalbaarheid van de aanbevelingen. De aanvaardbaarheid is geen probleem.

Onderbouwing

Achtergrond

De problematiek van patiënten die COVID-19 hebben doorgemaakt en die revalidatiezorg en -behandeling nodig hebben is vaak complex. Wat opvalt is de onvoorspelbaarheid van het verloop bij het herstel. Waar sommige patiënten onverwacht kunnen opknappen, blijft de revalidatie van andere patiënten achter. Soms zijn er klachten waarbij aanvullende diagnostiek nodig is. In vergelijking met andere patiëntengroepen zien we bij COVID-19 patiënten dat er vaker sprake is van hertriage en klachten waarvoor consultatie van andere zorgprofessionals nodig is. Omdat de problematiek van de patiënt op vele terreinen kan liggen, is de hulpvraag divers, en dat geldt daarmee ook voor de competenties en expertise die binnen het behandelteam aanwezig moeten zijn. In deze module wordt beschreven met welke specialismen op afroep een overleg- en/of doorverwijsmogelijkheid moet bestaan.

Zoeken en selecteren

Er is geen search uitgevoerd, omdat deze vraag zich moeilijk laat onderzoeken in de literatuur. Als studies er wel zouden zijn, dan is de kans zeer groot dat de studieresultaten niet van toepassing zijn op de Nederlandse situatie. De uitgangsvraag is daarom beantwoord met behulp van expertise van de werkgroep die uit verschillende disciplines bestaat. De aanbevelingen zijn gebaseerd op de beschreven overwegingen.

Verantwoording

Laatst beoordeeld : 24-09-2021

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Referenties

Federatie Medisch Specialisten, 2021. Leidraad Vervroegd ontslag COVID-19 patiënten met zuurstofbehoefte. Versie April 2021.

Startpagina - Voorlichting over het beloop, adviezen en diagnostiek in de eerste lijn bij COVID-19

Waar gaan deze richtlijnmodules over?

Deze richtlijnmodules (in herziening) beschrijven de zorg aan patiënten met langdurige (≥ 4 weken na infectie) klachten na COVID-19, onafhankelijk van de context waarin zij de ziekte hebben doorgemaakt.

In deze modules komen de volgende onderwerpen aan bod:

- Langdurig klachten na COVID-19: welke voorlichting en adviezen kunnen verwijzers aan patiënten geven?
- Welk aanvullend onderzoek (algemeen) wordt aanbevolen in de huisartsenpraktijk?
- De waarde van een ecg door de huisarts om relevante cardiale pathologieën aan te tonen dan wel uit te sluiten, bij patiënten met persisterende pijn op de borst of dyspneu bij inspanning na COVID-19.
- De waarde van een D-dimeertest door de huisarts om een longembolie bij patiënten met persisterende dyspneuklachten na COVID-19 uit te sluiten.
- De waarde van een (herhaalde) cognitiescreening door de huisarts ter objectivering of monitoring van cognitieve klachten na COVID-19.
- Wat er bekend is over de prevalentie van de belangrijkste aandoeningen (zoals diabetes mellitus) bij patiënten na doorgemaakte COVID-19.

Voor wie zijn deze richtlijnmodules bedoeld?

De module over de voorlichting aan patiënten (module Natuurlijk beloop) zijn vooral bedoeld voor verwijzers in het algemeen, anders dan specifiek alleen de huisarts. Deze aanbevelingen zijn niet van toepassing op patiënten die opgenomen zijn geweest in het ziekenhuis of een eerstelijnsverblijf met COVID-19 en behandeld worden binnen de medisch-specialistische revalidatie of geriatrische revalidatiezorg. De aanbevelingen in deze module komen overeen met de adviezen die worden gegeven in het onderdeel Voorlichting in de NHG-Standaard. De modules over het aanvullend onderzoek, de D-dimeertest, cognitieve screening en ecg zijn vooral bedoeld voor de huisarts.

In de verantwoording van elke module staat beschreven welke verenigingen en organisaties de desbetreffende module hebben geautoriseerd of geaccordeerd.

Voor patiënten

Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over COVID-19. Daarnaast is aanvullende informatie beschikbaar op het [Coronaplein](https://coronaplein.nl) en [C-support.nu](https://c-support.nu).

Hoe zijn deze richtlijnmodules tot stand gekomen?

Deze modules zijn ontwikkeld binnen het project 'Langdurige klachten na COVID-19'. In de verantwoording worden het ontwikkelproces en de samenstelling van de stuur-, werk- en klankbordgroep in detail beschreven.

Toepassing

Bij deze richtlijnmodules zijn een e-learning module en een webinar ontwikkeld. De e-learning is bedoeld voor

medisch specialisten (met name longartsen, klinisch geriaters, internisten en revalidatieartsen) en huisartsen en is op elk gewenst moment te starten. Deze is geaccrediteerd met 2 punten (ABAN). Op 2 juni 2022 vond een webinar plaats, waarin drie thema's uit de richtlijn worden uitgelicht met specifieke ervaringen en uitdagingen uit de praktijk. [Kijk deze hier terug](#), gebruik het wachtwoord 0a5W%pyi.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Natuurlijk beloop na COVID-19

Uitgangsvraag

Wat is bekend over het natuurlijk beloop van aanhoudende klachten na COVID-19?

Aanbeveling

Licht de patiënt in over het mogelijke beloop van de herstelperiode. Leg uit dat iedereen die COVID-19 heeft doorgemaakt langdurig klachten kan houden. Uitgaande van ongevaccineerde patiënten is ongeveer de helft na 3 maanden klachtenvrij.

Indien de patiënt in de eerste 6 weken na infectie wordt gezien

Bespreek dat gedurende de eerste 6 weken na COVID-19 de nadruk ligt op leefstijladviezen: adviseer voldoende te bewegen, maar adviseer ook voldoende rust, goede voeding, voldoende slaap en een matige tot geen alcoholinname.

Aanbevelingen onafhankelijk van tijdsperiode en afhankelijk van de klachten van de patiënt

Leg uit dat aanhoudende lichamelijke klachten gevolgen hebben op biologisch, psychologisch en sociaal gebied. Om deze reden is het belangrijk om aan al deze gebieden aandacht te besteden en zodoende factoren op te sporen die het herstel kunnen belemmeren.

Leg uit dat veel patiënten, naast lichamelijke klachten, ook psychische klachten, zoals angst, slaapproblematiek en somberheid kunnen ervaren, zonder dat hiervoor altijd een aanwijsbare oorzaak is. Leg hierbij eventueel uit dat lichaam en geest 1 geheel vormen en niet onafhankelijk van elkaar functioneren.

Besteed zo nodig aandacht aan de gesteldheid en het welzijn van naasten en mantelzorgers.

Wijs patiënten op de volgende websites:

- [Thuisarts.nl](https://thuisarts.nl). De informatie op [Thuisarts.nl](https://thuisarts.nl) is gebaseerd op deze richtlijn.
- [Coronaplein.nu](https://coronaplein.nu). Dit is het platform van de patiëntenorganisatie voor mensen met langdurige klachten na COVID-19.
- [C-support.nu](https://c-support.nu). Deze netwerkorganisatie ondersteunt mensen met > 3 maanden (complexe) klachten na COVID-19.

Onderbouwing

Achtergrond

Het herstel na COVID-19 is voor iedereen anders. Mensen met milde klachten kunnen binnen een week al beter zijn, maar kunnen ook weken- tot maandenlang last houden en regelmatig een terugval ervaren. Bij mensen die ernstigere klachten tijdens COVID-19 hebben gehad, en al dan niet opgenomen zijn geweest in het ziekenhuis, duurt het herstel veelal enkele weken, maar dit kan ook (veel) langer zijn. Het is van belang om goed in kaart te hebben welke klachten of schade kunnen persisteren na een doorgemaakte SARS-CoV-2-infectie, wat er voor nodig is om deze restklachten te herstellen en hoelang het herstel kan duren. In deze

module beschrijven we wat bekend is over het natuurlijk beloop van aanhoudende klachten na een SARS-CoV-2-infectie.

Samenvatting literatuur

NICE included 6 studies, three systematic reviews of highest quality (which included a range of 28-45 studies, with some overlap) and three large cohort studies (Nasserie, 2021; Domingo, 2021; Michelen, 2021; Whittaker, 2021; Taquet, 2021). The reviews had different study populations and different approaches to the analysis. For details see [NICE](#).

If possible, subgroup analyses were performed for hospitalized vs. non-hospitalized patients. The majority of studies were studies without a control group; describing the first three months after COVID-19 and were performed among patients that were hospitalized during COVID-19.

Table 1 shows the most important complaints and their frequencies, calculated from the included studies, per review and timeframe.

Table 1. Most important complaints and their frequencies, calculated from the included studies, per review and timeframe.

Sign or symptom	Nasserie, 2021	Domingo, 2021	Domingo, 2021	Michelen, 2021
	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 4 or more weeks Median frequency (IQR)	Population: COVID-19 positive reporting ongoing symptoms between 4-12 weeks Prevalence % (95% CI)	Population: COVID-19 positive reporting ongoing symptoms 12+ weeks Prevalence % (95% CI)	Population: Confirmed or suspected COVID-19 reporting ongoing symptoms at 12 or more weeks Proportion % (95% CI)
Fatigue	40% (31 to 57%) (25 studies)	51% (39% to 64%) (9 studies)	47% (27% to 68%) (3 studies)	31% (24% to 39%) (17 studies)
Dizziness	None reported	6% (0% to 5%) (1 study)	6% (5% to 7%) (1 study)	4.5% (2.5% to 7.9%) (5 studies)
Fever	1% (0 to 3%) (10 studies)	1% (0% to 5%) (4 studies)	0% (0% to 1%) (3 studies)	1.18% (0.2% to 4.7%) (7 studies)
Dyspnoea	36% (27.6% to 50%) (26 studies)	38% (27% to 51%) (10 studies)	22% (12% to 35%) (4 studies)	25.1% (17.9% to 34.0%) (20 studies)
Chest pain	13.1% (10.8% to 18%) (11 studies)	9% (4% to 19%) (2 studies)	5% (2% to 12%) (1 study)	6.4% (3.2% to 12.4%) (11 studies)
Palpitations	None reported	11% (5% to 16%) (1 study)	9% (8% to 11%) (1 study)	9.7% (6.0% to 15.3%) (8 studies)

Blocked nose	None reported	15% (10% to 20%) (1 study)	None reported	5.0% (2.7% to 8.9%) (3 studies)
Cough	16.9% (14.4% to 25.1%) (18 studies)	28% (22% to 35%) (6 studies, any type of cough)	6% (4% to 8%) (2 studies, dry cough only)	8.17% (4.85% to 13.44%) (16 studies)
Sore throat	None reported	7% (5% to 10%) (2 studies)	4% (2 to 8%) (2 studies)	4.7% (2.4% to 8.9%) (5 studies)
Voice change	None reported	20% (12% to 28%) (1 study)	None reported	8.2% (4.2% to 14.2%) (1 study)
Nausea	None reported	1% (0% to 3%) (1 study)	4% (1% to 8%) (1 study)	None reported
Diarrhoea	None reported	5% (3% to 7%) Prevalence % (95% CI) (3 studies)	2% (1% to 4%) (2 studies)	4% (2.1% to 7.6%) (10 studies)
Weight loss	None reported	12% (6% to 17%) (1 study)	None reported	21.0% (8.1% to 44.5%) (2 studies)
Joint pain	None reported	19% (14% to 25%) (3 studies)	9% (8% to 11%) (3 studies)	9.4% (5.7% to 15.1%) (9 studies)
Muscle pain	None reported	22% (16% to 28%) (1 study)	5% (2% to 12%) (3 studies)	11.3% (6.2% to 19.8%) (12 studies)
Headache	None reported	12% (10% to 15%) (3 studies)	4% (2% to 10%) (3 studies)	4.9% (2.3% to 10.1%) (11 studies)
Smell dysfunction	23.6% (12.4% to 40.7%) (12 studies)	13% (12% to 36%) (5 studies)	14% (9% to 22%) (3 studies)	15.2% (10.8% to 21.0%) (19 studies)
Taste dysfunction	15.6% (10.1% to 23.9%) (13 studies)	7% (5% to 11%) (3 studies)	10% (7% to 15%) (3 studies)	13.5% (9.0% to 19.9%) (17 studies)
Anxiety	22.1% (10% to 29.6%) (10 studies)	29% (16% to 48%) (2 studies)	23% (21% to 25%) (1 study, anxiety or depression)	18.7% (8.9% to 32.3%) (7 studies)
Depression	None reported	22% (19% to 25%) (2 studies)	None reported	8.1% (4.1% to 15.1%) (6 studies)
PTSD	None reported	22% (14% to 34%) (3 studies)	17% (8% to 27%) (1 study)	9.1% (3.7% to 21.0%) (6 studies)

Sleep disturbance	None reported	36% (10% to 74%) (2 studies)	26% (24% to 29%) (1 study)	18.2% (9.6% to 31.6%) (9 studies)
Memory problem	28.3% (18.6% to 35.8%) (5 studies)	19% (17% to 22%) (2 studies)	None reported	17.9% (5.3% to 46.3%) (5 studies)
Concentration difficulties	22% to 28% Range (4 studies)	25% (22% to 28%) (2 studies)	None reported	26.0% (21.0% to 31.7%) (2 studies)
Cognitive impairment	17.6% (15% to 21.6%) (6 studies)	24% (18% to 21%) (2 studies)	None reported	17.77% (0.08% to 98.23%) (3 studies)
Confusion	None reported	9% (5% to 13%) (1 study)	2% (1% to 4%) Prevalence % (95% CI) (1 study)	2.7% (1.9% to 3.8%) (2 studies)
Hair loss	None reported	10% (8% to 12%) (1 study)	22% (20% to 24%) (1 study)	14.3% (5.3% to 33.2%) (5 studies)

Most prevalent complaints overall were

- fatigue
- dyspnoea
- cough
- sleep disturbances
- anxiety and depression
- cognitive impairment
- concentration difficulties.

There was variation in symptoms prevalence at 4-12 weeks and 12+ weeks. Fatigue was commonly reported at both 4-12 weeks (51%) and 12 + weeks (47% and 31%). Concentration difficulties also remained prevalent over time (25% at 4-12 weeks and 26% at 12+ weeks). However, other commonly reported symptoms at 4-12 weeks, such as cough, sleep disturbance, anxiety and depressive symptoms appear to decrease in prevalence over time. Cough was much more prevalent at 4-12 weeks (28%) compared to 12 or more weeks (6% and 8%). Sleep disturbance was more prevalent at 4-12 weeks (36%) compared to 12 or more weeks (18% and 26%). This was similar for anxiety and depression. In contrast, hair loss was less prevalent at 4-12 weeks (10%) but more studies reported this symptoms at 12 or more weeks (14% or 22%).

Subgroup analysis

If possible, subgroup analyses were carried out in the reviews based on whether patients had been hospitalised or not for their acute illness. For fatigue there was higher prevalence in those who had previously been hospitalised (59% at 4-12 weeks; 37.1% and 63% at 12+ weeks) compared to those who had not been

hospitalised (16% at 4-12 weeks and 24.6% at 12+ weeks). This was similar for dyspnoea (hospitalised 57% at 4-12 weeks and 29% at 12+ weeks; nonhospitalised 24% at 4-12 weeks and 13.72% at 12+ weeks). Whittaker (2021) confirmed this.

Kwaliteit van bewijs

Het NICE beoordeelt de kwaliteit van het bewijs als matig tot zeer laag. Voor alle geïnccludeerde onderzoeken geldt dat er sprake is van een matig tot hoog risico op bias. Redenen voor dit risico op bias zijn onder meer loss to follow-up, het ontbreken van een controlegroep, kans op *recall bias* (vanwege zelfgerapporteerde uitkomsten) en de manier van deelnemersselectie. In een minderheid van de onderzoeken werden ook niet-PCR-bevestigde gevallen van COVID-19 meegenomen. De werkgroep schat de kwaliteit in als laag tot zeer laag, omdat het merendeel van de patiënten een matig tot ernstige acute fase doormaakten en/of gehospitaliseerd waren (extra afwaardering voor indirectheid). Tegelijkertijd worden symptomen als vermoeidheid en dyspneu consistent gerapporteerd in alle studies, wat de zekerheid over de prevalentie van deze symptomen vergroot.

Het NICE-panel was van mening dat het helpend kan zijn voor zowel arts als patiënt om een idee te hebben wat zij kunnen verwachten in het beloop van de ziekte. Hierbij dient uiteraard wel in acht genomen te worden dat het duidelijk is dat niet alle patiënten dezelfde klachten hebben en er dus ook geen strikte criteria voor langdurige klachten na COVID-19 gehanteerd moeten worden.

Conclusie

- Hoewel er veel onderzoeken zijn verricht, is de kwaliteit van bewijs matig tot zeer laag ten aanzien van het natuurlijk beloop van de klachten in de post-acute fase van COVID-19.
- De meest beschreven klachten zijn vermoeidheid (31-51%), dyspneu (22-38%), hoesten (6-28%), slaapproblemen (18-36%), angstklachten (19-29%), somberheidsklachten (8-22%) en cognitieve stoornissen (18-28%).
- Hoesten, slaapproblemen en angst- en somberheidsklachten kwamen minder vaak voor in de periode ≥ 3 maanden na COVID-19, terwijl de prevalentie van vermoeidheid en cognitieve stoornissen ongeveer gelijk blijft door de tijd heen.
- Patiënten die tijdens de acute fase gehospitaliseerd waren, rapporteerden vaker vermoeidheids- en benauwdheidsklachten in vergelijking tot patiënten die dat niet waren.

Zoeken en selecteren

Voor de uiteenzetting van het bewijs is gebruik gemaakt van de NICE-richtlijn 'COVID-19 rapid guideline: managing the long-term effects of COVID-19 (laatste update: november 2021).

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

National Institute for Health and Care Excellence. COVID-19 rapid guideline: managing the long-term effects of COVID-19 (NG188): Evidence reviews 2 and 3: prevalence. NICE Guideline nummer 188. London: National Institute for Health and Care Excellence, 2021.

Aanvullend onderzoek (algemeen) na COVID-19

Uitgangsvraag

Welke diagnostiek wordt aanbevolen bij patiënten met aanhoudende klachten na COVID-19 in de huisartsenpraktijk?

Aanbeveling

Er zijn geen aanwijzingen dat oriënterend laboratoriumonderzoek, X-thorax of spirometrie in de huisartsenpraktijk bijdragen aan het aantonen dan wel uitsluiten van COVID-19 gerelateerde pathologie. Verricht gericht aanvullend onderzoek uitsluitend om andere aandoeningen aan te tonen/uit te sluiten. Voor bepaalde patiëntengroepen (patiënten met aanhoudende dyspneuklachten, aanhoudende pijn op de borst en/of aanhoudende cognitieve problemen) na COVID-19 zijn aparte aanbevelingen geformuleerd. Zie hiervoor de betreffende modules ([D-dimeer](#), [ECG](#), [Cognitieve screening](#)).

Onderbouwing

Achtergrond

Het herstel na COVID-19 is voor iedereen anders. Mensen met milde klachten in de acute fase kunnen binnen een week al beter zijn, maar kunnen ook weken- tot maandenlang last houden en regelmatig een terugval ervaren. Bij mensen die ernstigere klachten hebben gehad, en al dan niet opgenomen zijn geweest in het ziekenhuis, duurt het herstel veelal enkele weken, maar dit kan ook langer zijn. Het is van belang om goed in kaart te hebben welke klachten of schade er kunnen persisteren na een doorgemaakte SARS-CoV-2-infectie, wat er voor nodig is om deze restklachten te herstellen en hoelang het herstel kan duren. In deze module beschrijven we wat bekend is over resultaten van aanvullende diagnostiek verricht na SARS-CoV-2-infectie.

Conclusies / Summary of Findings

- Er is nog zeer weinig bekend over de waarde van aanvullend onderzoek in de post-acute fase van COVID-19.
- We zijn onzeker, maar X-thorax is mogelijk geen goede marker van herstel (kwaliteit van bewijs: zeer laag).

Samenvatting literatuur

NICE included 18 references in their review, concerning 15 studies that reported on the results of supplementary examinations and/ or diagnostics during the period between 4 and 12 weeks after COVID-19: 11 cohort studies, 2 cross-sectional studies, 1 case-control study and one case-report. Additionally, there was one cohort study reporting on this covering the period >12 weeks after COVID-19. Lastly, they included 1 narrative review and 1 expert opinion.

The supplementary literature search yielded four additional cohort studies.

Hospitalized patients

Psychological health

Four studies reviewed psychological health, using screening instruments, all found abnormal / raised values in

post-COVID-19 patients. One study (Raman, 2021) reported that this was significantly more compared to a non-infected group of matched controls (2-3 months post-COVID-19, PHQ-9 score).

Functional assessment

Three studies reported on functional assessment. Raman (2021; again the only one using a control group) concluded that 2-3 months post-COVID-19 functional status (including physical and social functioning) was significantly worse compared to those that did not suffer from COVID-19.

Imaging studies

Many studies used imaging when following up patients after COVID-19. This was mostly X-thorax, CT and MRI; one study (D'Cruz, 2021; only hospitalized patients) reported COVID-19 related lung disease (as found on X-thorax) in 15/119 patients (13%). However, the same study also concluded X-thorax to be an unreliable marker for recovery, considering that any abnormalities on CT were not related to the presence of abnormalities on X-thorax. A Chinese study (Liu, 2021) investigated 41 post-COVID-19 patients who had been hospitalized and undergone CT imaging during hospitalization by performing a follow-up CT scan at 3 months and 7 months after discharge. They concluded that the majority of patients did not have any abnormalities on CT scan anymore at the last moment of follow-up (66% for the complete group, 86% if only including those without signs of pulmonary fibrosis). In an English study (Sykes, 2021; n=125, hospitalized patients, median follow-up 113 days) 77% of the post-COVID-19 patients had a normal X-ray, 8% had a decrease of >50% of the abnormalities, and the remainder had persisting non-COVID-19 related deviations. A Chinese study (Li, 2021; n=107 post-hospitalized patients, 100 days after discharge), on the other hand reported complete resolution of pulmonary abnormalities (CT thorax) in only 28%.

Pulmonary function tests

Spirometry and or Medical Research Council Breathlessness Scale were used frequently in the included studies. One study used a COVID-negative control group (Raman, 2021), and found that hospitalized post-COVID-19 patients more frequently had increased scores for dyspnoea 2-3 months after infection (MRC dyspnoea score ≥ 2) compared to patients not having suffered from COVID-19 (36/53 [64%] vs. 3/29 [10.3%], $p < 0.0001$). The same study found a minimal difference in FEV₁/FVC (0.77 vs 0.75, $p = 0.027$) between post-COVID-19 patients and controls; FVC and FEV₁ individually were not significantly different. Other studies (not using a control group) showed varying results on spirometry (mild abnormalities in ~25-55%), in general not related to the severity of disease during the acute phase.

Additionally, exercise tests were performed, during which exercise tolerance and desaturation (during physical exercise) were measured in patients post-COVID-19. One Italian study (Bellan, 2021; n=238, average age 68, 60% male, all hospitalized patients), performed a pulmonary function test in 224 post-COVID-19 patients 3-4 months after hospital discharge, finding a decreased diffusion capacity in 52% (D_{LCO} <80% of expected). In 16% this was as bad as <60% of expected.

Laboratory investigations

Investigated laboratory values mostly concerned inflammatory parameters, markers for iron deficiency and anaemia or lipid profile. Dennis (2011) found (in unadjusted analysis) abnormal triglycerides ($p = 0.002$),

cholesterol ($p=0.021$), LDL-cholesterol ($p=0.005$) and transferrin saturation ($p=0.005$) in hospitalized patients after COVID-19. Li (2021; China, $n=107$, 100 days after discharge), had a similar conclusion; they found raised LDL-c and HCL values in patients that survived severe tot critical COVID-19.

Non-hospitalized patients

None of the included studies only included non-hospitalized patients. There were a few studies that had a combined population of hospitalized and non-hospitalized post-COVID-19 patients.

Pulmonary function tests

Two studies described spirometry in post-COVID-19 patients, also including non-hospitalized patients. Frijia (2020; 18% non-hospitalized patients) found no association between the result of the spirometry and the severity of abnormalities on CT-thorax. Valiente (preprint, included in NICE review) performed spirometry in 32/108 patients 12 weeks after the acute phase, which was abnormal in 28% of the patients (mostly showing an obstructive).

Functional status

One study (Aliae, preprint, included in NICE review) included 98 (24%) non-hospitalized patients and described basic daily functioning using the new post-COVID-19 functional status assessment (PCFS). In this study 11 patients (2.5%) reported moderate to severe limitations in functioning.

Imaging

None of the included studies described imaging in non-hospitalized patients post-COVID-19.

Laboratory investigations

Dennis (2021) reported on differences between hospitalized and non-hospitalized post-COVID-19 patients (see in section 'hospitalized patients'). Sonnweber (2020; 20% non-hospitalized patients) reported that iron homeostasis was more frequently abnormal post-COVID-19. Additionally they reported an association between the level of ferritin and the severity of acute illness.

Kwaliteit van bewijs

De beschreven onderzoeken zijn van zeer lage kwaliteit en hebben relatief lage patiënten aantallen (grotendeels < 500 patiënten). Geen van de onderzoeken was specifiek ontworpen om de onderzoeksvraag te beantwoorden en deze dienen dus enkel als indirect bewijs. Het risico op bias wordt op 1 onderzoek (matig) na bij alle onderzoeken hoog ingeschat. Redenen hiervoor zijn onder andere het ontbreken van een controlegroep (of een vergelijking met pre-COVID-19-status) en risico op selectiebias. Daarnaast wordt de generaliseerbaarheid zeer laag geacht, gezien het feit dat de onderzoeken voornamelijk 1) in de tweede lijn werden gedaan (in totaal < 10% niet-gehospitaliseerde patiënten), 2) met een beperkte follow-up (meestal 4-6 weken) en 3) geen kinderen/ouderen beschreven.

Zoeken en selecteren

Voor de uiteenzetting van het bewijs is gebruik gemaakt van de NICE-richtlijn 'COVID-19 rapid guideline: managing the long-term effects of COVID-19. Evidence review 4: investigations (laatste update: december 2020). Op 14 april 2021 is een aanvullende literatuurzoekactie naar systematische reviews (SR's), randomized

controlled trials (RCT's) en observationeel onderzoek uitgevoerd in PubMed en Embase.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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ECG na COVID-19

Uitgangsvraag

Is een ecg aan te bevelen voor het uitsluiten van relevante cardiale pathologieën (myocarditis, pericarditis) bij COVID-19-patiënten met ≥ 4 weken aanhoudende klachten van pijn op de borst of dyspneu bij inspanning in de huisartsenpraktijk?

Aanbeveling

Wees terughoudend met ecg-onderzoek om myocarditis en/of pericarditis aan te tonen dan wel uit te sluiten bij patiënten met aanhoudende pijn op de borst na COVID-19. Een normaal ecg sluit deze diagnoses niet uit.

Overwegingen

Voor- en nadelen van de interventie

Het is onbekend of het zinvol is om een ecg te maken bij patiënten met aanhoudende klachten van pijn op de borst en/of dyspneu na COVID-19 voor het uitsluiten van relevante cardiale pathologieën. We vonden alleen 1 kleine studie die de accuratesse van een ecg voor het aantonen van myocarditis beschreef bij patiënten ≥ 3 maanden na ontslag uit het ziekenhuis en hersteld van COVID-19.

Kwaliteit van bewijs

Laag, vanwege afwaardering voor risk of bias en onnauwkeurigheid; kleine onderzoeken waarbij niemand myocarditis had. Er is niet afgewaardeerd voor indirect bewijs, omdat het bij 2 van de 3 onderzoeken patiënten met aanhoudende klachten betrof.

Waarden en voorkeuren van patiënten

Het maken van een ecg kent weinig nadelen; het is non-invasief en heeft geen risico op complicaties (behalve eventuele beschadiging van de huid bij het verwijderen van ecg-plakkers). Daarbij wegen voor de meeste mensen de nadelen, zoals bijvoorbeeld de tijdsinvestering en eventuele kosten (indien het eigen risico nog niet is opgebruikt) op tegen de eventuele voordelen van het uitsluiten van mogelijk ernstige pathologie. Bij toenemende onzekerheid over de waarde van het ecg neemt de bereidheid van patiënten mogelijk enigszins af.

Kosten

De kosten voor het maken van een ecg bij de huisarts liggen rond de € 50. Indien het ecg gemaakt wordt bij een diagnostisch centrum (zoals Saltro), liggen de kosten hoger: rond de € 80-90.

Aanvaardbaarheid

Voor de meerderheid van de mensen is een ecg een aanvaardbare optie.

Haalbaarheid

Op dit moment is het gebruik van een ecg test als diagnosticum in de huisartsenpraktijk al zeer gangbaar. Het wisselt per praktijk (en eventueel per indicatie) of een ecg kan worden afgenomen in de praktijk zelf of dat hiervoor wordt doorverwezen naar een diagnostisch centrum of de polikliniek in het ziekenhuis.

Waarom deze aanbeveling?

Er is geen wetenschappelijk bewijs dat een ecg zinvol is bij patiënten met aanhoudende klachten van pijn op de borst of dyspneu na COVID-19 om relevante COVID-19 gerelateerde cardiale pathologie aan te tonen dan wel uit te sluiten. Er zijn aanwijzingen dat afwijkingen die op het ecg worden gezien niet specifiek genoeg en ongeschikt zijn hiervoor. Om deze reden adviseren we terughoudendheid ten aanzien van het routinematig verrichten van een ecg bij patiënten met aanhoudende klachten na COVID-19.

Onderbouwing

Achtergrond

Om te bepalen of er sprake is van myocarditis en/of pericarditis kan een arts verschillende onderzoeken uitvoeren: algemeen lichamelijk onderzoek en bloedonderzoek, ecg, cardiale MRI, SPECT-scan, echografie of hartbiopsie. Het ecg is een eenvoudig diagnostisch hulpmiddel. Ecg-veranderingen (hartritmestoornissen of repolarisatie-afwijkingen) dragen mogelijk bij aan de diagnose myocarditis. Een biopsie uit het hart is de gouden standaard, maar gezien het risico gebeurt dit niet vaak. Daarom worden verschillende criteria gebruikt om de diagnose op indirecte wijze te stellen. Cardiale MRI is de beeldvormende modaliteit die de voorkeur heeft voor de niet-invasieve evaluatie van myocarditis en/of pericarditis. In deze module beschrijven we wat bekend is over de waarde van een ecg voor het aantonen dan wel uitsluiten van relevante cardiale pathologieën bij patiënten met aanhoudende cardiale klachten ≥ 4 weken na COVID-19.

Conclusies / Summary of Findings

- Two small studies described both ECG assessment and CMR in adults ≥ 4 weeks after COVID-19 *with persisting symptoms*. Both studies are suggestive that ECG findings are not useful in ruling out myocarditis (quality of evidence: low).
- Two studies described the yield of an ECG assessment by matters of *routine testing* in adults ≥ 4 weeks after COVID-19. Abnormalities seen on ECG seem non-specific and unable to adequately assess for relevant cardiac pathologies.

Samenvatting literatuur

No systematic reviews or primary research was found that met the criteria for inclusion. In the search update one systematic review was checked for relevant references, but none were relevant.

As none of the studies fulfilled all pre-specified criteria, we decided to describe studies that performed ECG registration in adult patients ≥ 4 weeks after COVID-19 illness, by matters of routine testing (Sechi, 2021, Wang, 2021), so disregarding specific presenting symptoms and if cardiovascular magnetic resonance (CMR) was performed or not.

The search update yielded two additional studies that performed both ECG and CMR in adult patients ≥ 4 weeks after COVID-19 (Breitbart, 2021, Kravchenko, 2021).

ECG registration and CMR

Wang (2021) examined consecutive patients recovered from COVID-19 >12 weeks after discharge irrespective of cardiac symptoms (n=44; China; mean age 48 year; 43% men). Cardiac screening included an

ECG and cardiovascular magnetic resonance (CMR). They detected myocardial injury (manifested as late gadolinium enhancement) in 13 COVID-19 patients (30%), while only 1 patient had abnormal ECG findings. Data of healthy control subjects were used as a comparison on certain CMR characteristic.

Kravchenko (2021) examined 41 post-COVID-19 patients (mean age 39 years, 43% men) with persistent symptoms like fatigue, or exertional dyspnoea. Median time between COVID-19 and examinations was 103 days. All underwent both CMR as well as ECG. All ECG results were normal. CMR results did not show edema in any of the patients. Three (7%) showed non ischemic LGE lesions, but without other Lake Louise criteria, thus not consistent with myocarditis.

Breitbart (2021) examined 56 post-COVID-19 patients, with persistent symptoms 71 +/- 66 days after COVID-19 as chest pain, (exertional) dyspnoea (suspected myocarditis). All received both ECG and CMR. Nine patients had CMR results that were suspicious for myocarditis, but of only one these could be confirmed as myocarditis (others did not fulfil Lake Louise criteria of ECG, echocardiogram and lab). This case did not have suspicious ECG findings. In total 3 had suspicious ECG findings (ST deviations), but none of these had myocarditis.

ECG registration, no CMR

Sechi (2021) examined 105 discharged COVID-19 patients (27 [26%] had severe COVID-19 required mechanical ventilation) that consecutively attended scheduled outpatient follow-up visits irrespective of cardiac symptoms (n=105, Italy, median follow-up 41 days, mean age 57 years, 47% women, >10% symptoms, 61% attended follow-up visits). No significant differences were detected in ECG tracings and structural and functional characteristics between patients who had recovered from mild-to-moderate or severe illness. In addition, in these patients, cardiac structure and function that were assessed by two-dimensional, Doppler, and TDI echocardiography did not differ from controls who were matched for age, sex, body mass index, blood pressure, and major coexisting conditions.

Zoeken en selecteren

Clinical question

Is an ECG recommended to rule out relevant cardiac pathologies (myocarditis, pericarditis) in COVID-19 patients with persistent chest pain or dyspnoea on exercise ≥ 4 weeks in primary care?

PICO:

P: Adults with persistent chest pain or dyspnoea on exercise 4 weeks from onset of COVID-19 in primary care

I: 12-lead ECG

R: Cardiovascular magnetic resonance (CMR)

O: Test accuracy (sensitivity, specificity, positive predictive value, negative predictive value), myocarditis, pericarditis, other relevant cardiac pathologies

Other selection criteria:

Study design: systematic reviews, RCTs, observational research. Follow-up: cross-sectional design

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms

from 2020 until 7-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO. The appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion.

The search was updated on August 30th 2021.

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Relevant outcome measures

A priori, the working group did not define the outcome measures listed above.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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D-dimeer na COVID-19

Uitgangsvraag

Is een D-dimeertest aan te bevelen voor het uitsluiten van een longembolie bij patiënten met doorgemaakte COVID-19 en ≥ 4 weken aanhoudende dyspneuklachten in de huisartsenpraktijk, uitgaand van een lage Wells-score?

Aanbeveling

Vraag alleen een D-dimeerbepaling aan bij patiënten met vermoeden van een longembolie, na een risico-inschatting en volgens de NHG-Standaard 'Diepveneuze trombose en longembolie'

Indien er (conform de NHG-Standaard) een D-dimeerbepaling is verricht:

- Bij een lage Wells-score en een negatieve D-dimeerbepaling kan veilig afgewacht worden.
- Bij een lage Wells-score en een verhoogde D-dimeerbepaling (> 500 ng/ml): overleg met de longarts.

Overwegingen

Voor- en nadelen van de interventie

Het is onbekend of het zinvol is om een D-dimeerbepaling te verrichten bij patiënten met aanhoudende dyspneuklachten na COVID-19 voor het uitsluiten van een longembolie.

Kwaliteit van bewijs

Er zijn geen onderzoeken over de accuratesse van een D-dimeerbepaling bij patiënten na doorgemaakte COVID-19 voor het uitsluiten van een longembolie.

Waarden en voorkeuren van patiënten

Voor de meeste mensen wegen de nadelen van een bloedbepaling (tijdsinvestering, minimaal invasief, klein risico op complicaties, eventuele kosten) op tegen de eventuele voordelen van het uitsluiten van mogelijk ernstige pathologie. Bij toenemende onzekerheid over de waarde van de uitslag van de bloedbepaling neemt de bereidheid van patiënten naar verwachting enigszins af.

Kosten

De kosten van een normale D-dimeerbepaling liggen bij klinische laboratoria rond de € 10-12. Voor 'point-of-care'-metingen is dit vergelijkbaar. Er zijn echter ook kosten verbonden aan het traject na de D-dimeerbepaling indien deze positief uitvalt. Bij deze patiënten vindt namelijk vervolgonderzoek plaats in de tweede lijn. De werkgroep schat op basis van de beschikbare literatuur in dat de grootte van deze groep niet groter is dan de 'normale' populatie die een D-dimeerbepaling ondergaat. De werkgroep verwacht dat die groep maximaal 25-35% van de patiënten betreft bij wie het D-dimeer wordt gemeten. De precieze kosten van een eventueel natraject zijn voor elke individuele patiënt verschillend, maar bedragen minimaal enkele honderden euro's.

Aanvaardbaarheid

De meerderheid van de mensen zal een bloedbepaling aanvaardbaar vinden.

Haalbaarheid

Op dit moment is een D-dimeerbepaling in de huisartsenpraktijk al zeer gangbaar, onder meer omdat de test aanbevolen wordt in de NHG-Standaard Diep veneuze trombose en longembolie.

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Waarom deze aanbeveling/rationale?

Er is geen wetenschappelijk bewijs dat een D-dimeer bepaling zinvol is bij patiënten met aanhoudende dyspneuklachten na COVID-19 voor het uitsluiten van een longembolie. Veel patiënten met aanhoudende klachten zullen uiteindelijk naar de longarts worden verwezen. Bij patiënten met progressieve dyspneu speelt er wel een (sub)acute component en kan een D-dimeer overwogen worden.

Er zijn geen aanwijzingen dat de huidige afkapwaarde van D-dimeer (500 ng/ml) onveilig zou zijn (inschatting werkgroep). COVID-19 zorgt eerder voor een verhoging dan een verlaging van het D-dimeer. Dit vergroot bij het hanteren van dezelfde afkapwaarde het risico op (te) veel CT-angiografieën en/of V/Q-scans. Gezien de aantallen lijkt dit risico mee te vallen en levert minder gezondheidsrisico's op voor de patiënt, zoals onterechte blootstelling aan röntgenstraling versus het missen van een eventuele klinisch relevante longembolie (inschatting werkgroep).

Onderbouwing

Achtergrond

Huisartsen worden regelmatig geconfronteerd met patiënten met benauwdheidsklachten. Inmiddels is bekend dat bij een aanzienlijk deel van de patiënten die COVID-19 hebben doorgemaakt benauwdheidsklachten in meer of mindere mate kunnen persisteren. Dit kan, zeker bij verergering, aanleiding geven tot diagnostische onzekerheid. Een gevreesde diagnose is bijvoorbeeld een longembolie. In de huisartsenpraktijk wordt D-dimeer vaak gebruikt om een longembolie uit te sluiten indien er een lage verdenking hierop bestaat (lage Wells-score). Gezien de interactie van het SARS-CoV-2-virus en het coagulatiesysteem is het de vraag of de betrouwbaarheid van D-dimeer om een longembolie uit te sluiten ook van toepassing is op patiënten die COVID-19 hebben doorgemaakt. In deze module beschrijven we wat bekend is over de waarde van een D-dimeerbepaling voor het uitsluiten van een longembolie bij patiënten met doorgemaakte COVID-19 en aanhoudende dyspneuklachten ≥ 4 weken na COVID-19. Patiënten met een hoge Wells-score vallen buiten de scope van deze module omdat een D-dimeerbepaling daar überhaupt niet bij geïndiceerd is gezien de hoge voorafkans op een longembolie.

Conclusies / Summary of Findings

- We found no studies that described the yield of D-dimer testing for pulmonary embolism ≥ 4 weeks after COVID-19 (regardless the presence of any dyspnoea).
- We found six studies that assessed D-dimer levels ≥ 4 weeks after for COVID-19 (mixed populations discharged or recovered at home). All studies did describe elevated D-dimer levels in post-COVID-19 patients, in roughly a quarter to a third of the patients (10% in one study). In three studies pulmonary embolism testing was performed on indication, all excluding pulmonary embolism.

Samenvatting literatuur

No systematic reviews or primary research was found that met the criteria for inclusion.

As none of the studies fulfilled all pre-specified criteria, we decided to describe studies that tested for D-dimer in adult patients ≥ 4 weeks after COVID-19, by matters of routine testing, so disregarding specific presenting symptoms and if pulmonary embolism testing was performed or not.

The search update yielded one additional study that performed D-dimer testing in adult patients ≥ 4 weeks after COVID-19 (Skala, 2021).

D-dimer with pulmonary embolism testing

Townsend (2021) investigated 150 (69 hospitalised [46%], of which 16 in ICU) consecutively enrolled post-COVID-19 patients at a minimum of 6 weeks after hospital discharge or symptom resolution ($n=150$, Ireland, median follow-up 81 days, mean age 47 years, 57% women, 63% still experienced breathlessness). In 38 patients (25%) D-dimer levels were elevated (higher than 500mg/ml, median level 327 ng/ml) at follow-up; 11 of these patients were in the non-hospitalised group. 8 patients (all with elevated D-dimer) underwent CT pulmonary angiogram (CTPA) based on clinical findings, but none revealed pulmonary embolisms (PE). One patient (in elevated D-dimer group) later presented with bilateral PE. Additionally, there was no relationship between ongoing breathlessness and elevated D-dimer level in multivariate analysis (beta coefficient -0.33 [95% CI -1.45 –0.79]). Patients with elevated D-dimer did have a 3.12 (95% CI 0.87-11.13) tendency to have an abnormal chest X-ray result. CRP had normalized in >90% of the patients at follow-up.

Daher (2020) investigated 33 hospitalised non-ICU post-COVID-19 patients on routine basis at 6 weeks after hospital discharge (Germany, tertiary hospital, mean age 64 years, 33% women). At that time 11 (33%) were still experiencing dyspnea. The median D-dimer level was 474 ng/ml (IQR 323-675) at follow-up. C-reactive protein values had normalized in virtually all patients at follow-up (average 2 mg/L, IQR 1.1-7.9). Patients with elevated D-dimer levels underwent V / Q scan, excluding pulmonary embolism in all patients.

Skala (2021; short report) described an ongoing cohort study, with preliminary results of 102 post-COVID-19 patients (Czechia, mean age 47 years, 54% female, 15% hospitalized). All underwent, among other investigations D-dimer testing. In case of elevated D-dimer CT angiography was performed. In total 10% of the patients had elevated D-dimer at three months post-COVID-19. No pulmonary embolisms were found.

D-dimer without pulmonary embolism testing

Venturelli (2020) routinely investigated 767 post-COVID patients (678 hospitalized [88%], of which 66 in ICU), 2-3 months after hospital/ED discharge ($n=767$, Italy (Bergamo), median follow-up 81 days, mean age 63 years, 33% women, 49% no symptoms). No pulmonary embolism testing was performed. The mean D-dimer value at follow-up was 700 ng/ml; 290 (37.8%) patients had D-dimer values higher than 500 mg/ml. C-reactive protein values had normalized in virtually all patients at follow-up.

Mandal (2020; brief communication) investigated 384 hospitalised (of which 54 in ICU [15%]) post-COVID-19 patients at a median of 54 days following hospital discharge (post COVID-19 follow-up service, England, mean age 60 years, 38% women). At this time 53% reported ongoing breathlessness; there was a trend in

decreasing breathlessness with increasing follow-up time. The average D-dimer level at follow-up (performed in 45%) was 384 ng/ml (IQR 242-665 ng/ml), with elevated values in 30.1% in those tested. C-reactive protein values had normalized in >90% of tested patients (n=332) at follow-up. No pulmonary embolism testing was performed.

Sibila (2021; letter to editor, possibly non-peer reviewed) investigated 172 hospitalized (of which 74 in ICU [43%]) COVID-19 patients 3 months after hospital discharge (Spain, mean age 56 years, 43% women). At that time 39.5% of the patients still experienced dyspnea. The average D-dimer value at 3 months was 582.6 ng/ml. In patients with lung function sequelae (carbon monoxide lung diffusion capacity <80% of reference) values were higher (697.6 ng/ml). C-reactive protein values had normalized in virtually all patients at 3 months. No pulmonary embolism testing was performed.

Zoeken en selecteren

Clinical question

Is a D-dimer blood test recommended to rule out pulmonary embolism in post-COVID-19 patients with persisting dyspnoea ≥ 4 weeks in primary care?

PICO:

P: Adults with persisting dyspnoea ≥ 4 weeks from onset of COVID-19 (low Wells score)

I: D-dimer (laboratory and point-of-care-testing)

R: Spiral-CT / CT-angiography

O: Test accuracy (sensitivity, specificity, positive predictive value, negative predictive value), pulmonary embolism

Other selection criteria

Study design: systematic reviews, RCTs, observational research. Follow-up: cross-sectional design

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 23-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO. The appendices (*Bijlagen*) contain the [PRISMA flowchart](#) showing the number of hits, and the reasons of exclusion. Based on the title and abstract screening, we found no study that met the criteria for inclusion in this summary of literature.

The search was updated on August 31st 2021.

Relevant outcome measures

A priori, the working group did not define the outcome measures listed above.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Cognitieve screening na COVID-19

Uitgangsvraag

Is een (herhaalde) cognitiescreening (I) aan te bevelen bij patiënten met doorgemaakte COVID-19 en aanhoudende cognitieve klachten ≥ 4 weken (bijvoorbeeld concentratie- en/of geheugenstoornissen, 'brain fog') (P) in de huisartsenpraktijk?

Aanbeveling

Vraag bij cognitieve klachten en/of overprikkelingsverschijnselen naar:

- ontstaanswijze, duur, progressie en beloop van de klachten
- concentratie- of geheugenstoornissen, vergeetachtigheid
- prikkelbaarheid, overgevoeligheid voor zintuiglijke prikkels
- problemen met plannen, organiseren

Wees terughoudend met (herhaalde) cognitiescreening door middel van een kort screeningsinstrument (zoals MOCA) bij patiënten met doorgemaakte COVID-19 en aanhoudende cognitieve klachten ≥ 4 weken (bijvoorbeeld Concentratie- en/of geheugenstoornissen) in de huisartsenpraktijk.

Overwegingen

Voor- en nadelen van de interventie

Er zijn aanwijzingen dat cognitieve klachten frequent voorkomen bij patiënten die COVID-19 doorgemaakt hebben. Ze kunnen worden opgespoord middels een goede anamnese gericht op cognitieve functies en de betekenis voor het dagelijks leven.

Kwaliteit van bewijs

De kwaliteit van het bewijs is zeer laag. Het betreft een observationeel onderzoek met kleine patiëntenaantallen of het ontbreken van een controlegroep (case series). Bovendien betreft het voornamelijk patiënten die opgenomen zijn geweest.

Waarden en voorkeuren van patiënten

Patiënten met aanhoudende cognitieve klachten na COVID-19 zullen over het algemeen openstaan voor een korte cognitieve anamnese/screening om de ernst en aard van de klachten in kaart te brengen.

Kosten

De kosten van het uitvoeren van een korte cognitieve anamnese/screening door een (medewerker van de) huisarts zijn beperkt in vergelijking met het uitvoeren van een uitgebreid neuropsychologisch onderzoek (inschatting van de werkgroep).

Aanvaardbaarheid

Een korte cognitieve anamnese/screening is voor de meerderheid van de mensen acceptabel.

Haalbaarheid

Tijdgebrek in de eerstelijnssetting kan een probleem zijn. Eventuele kennistekorten bij het toepassen en interpreteren van een cognitief screeningsinstrument kunnen relatief gemakkelijk worden opgelost (inschatting van de werkgroep).

Waarom deze aanbeveling/rationale?

Er zijn aanwijzingen dat COVID-19 kan leiden tot cognitieve klachten, zoals geheugenproblemen en concentratiegebrek. Het is van belang dat de huisarts dit soort klachten serieus neemt. Het afnemen van een goede anamnese gericht op cognitieve functies en betekenis voor het dagelijks leven kan de huisarts helpen om de ernst van de klachten goed in te schatten. We zijn onzeker of een kort screeningsinstrument zoals MOCA hier iets aan toevoegt.

Onderbouwing

Achtergrond

Er zijn aanwijzingen dat COVID-19 kan leiden tot aanhoudende cognitieve klachten, zoals geheugenproblemen en concentratiegebrek. Voor het in kaart brengen van cognitieve klachten is een grote range aan meetinstrumenten beschikbaar. De meeste zijn echter zeer uitgebreid of vergen een getrainde zorgverlener die het afneemt, waardoor ze ongeschikt zijn voor de huisartsenpraktijk. Het is dus (nog) onduidelijk hoe de huisarts het beste de ernst van de cognitieve klachten objectief in kaart kan brengen en/of kan vervolgen. In deze module beschrijven we wat bekend is over de resultaten van (herhaalde) cognitiescreening bij patiënten met aanhoudende cognitieve klachten ≥ 4 weken na COVID-19.

Conclusies / Summary of Findings

- Cognitive impairments were reported by approximately one quarter of post-COVID-19 patients when assessed with a single cognitive screening test (quality of evidence: very low).
- Cognitive screening tests that were used were the Montreal Cognitive Assessment (MoCA, objective measurement [impaired/unimpaired]), Telephone Interview of Cognitive Status (TICS, objective measurement) and the Cognitive Failure Questionnaire (CFQ-25, subjective measurement [low/high]).
- We found no research that repeated cognitive testing over time.

Samenvatting literatuur

No systematic reviews or primary research was found that met the criteria for inclusion. The search for primary research yielded four studies that are described below.

The search update yielded one additional study (Liu, 2021).

Morin (2021) systematically performed a telephone assessment in survivors of COVID-19 four months after hospital discharge (n=478, France, mean age 61, 58% male, 30% ICU patients). Respiratory, functional and cognitive symptoms were assessed; cognitive symptoms were assessed with the Q3PC cognitive screening questionnaire (e.g. three questions on memory difficulties, mental slowness, concentration problems). Among the 1151 adult patients hospitalized, 834 were eligible for telephone assessment and 478 (57%) consented. Cognitive problems were frequent: 21% (86/416) of the patients reported at least 1 cognitive symptom. All patients who still had symptoms were invited for further evaluation in the ambulatory setting (n=177, 55% ICU).

patients). Global cognitive assessment was performed with the Montreal Cognitive Assessment (MoCA, 11 items, takes approximately 10 minutes). Attention was assessed through the d2-R test (instrument for measuring visual attention, information processing speed and the ability to concentrate). Memory complaints were assessed through the McNair self-questionnaire. Cognitive impairment was confirmed in 38% (61/159).

Raman (2021) investigated cognitive functioning as part of a multidisciplinary evaluation at the outpatient clinic in survivors of moderate to severe COVID-19 2-3 months after hospital discharge (n=58, UK, mean age 55, 59% male) and in 30 matched controls. Cognitive function was assessed using the Montreal Cognitive Assessment (MoCA). Patients demonstrated impaired cognitive performance, specifically in the executive and visuospatial domains. 28% (16/58) of the patients had a total MoCA score that was abnormal according to the established cut-off of <26, compared to 17% (5/30) of controls.

Woo (2020) assessed cognitive deficits in young, mild to moderate COVID-19 patients who visited an outpatient clinic for post-COVID-19 care (n=18, Germany, mean age 42, 42% male) and 10 age-matched healthy controls. Patients and controls were interviewed with the Modified Telephone Interview of Cognitive Status (TICS-M), in person or by phone. This screening instrument consists of 12 items (TICS-M, total score 50 points, takes approximately 15-20 minutes). Post-COVID-19 patients scored significantly lower results in the TICS-M (mean, 38.8; range, 31–46) compared to healthy controls (mean, 45.8; range, 43–50), especially regarding short-term memory, attention and concentration/language tasks.

De Graaf (2021) evaluated cognitive functioning as part of a multidisciplinary evaluation in COVID-19 patients at the outpatient clinic 6 weeks after hospital discharge (n=81, the Netherlands, mean age 61, 63% male). Patients filled out the Cognitive Failure Questionnaire (CFQ-25, 25 questions, takes approximately 5-10 minutes) and patients' partners/caregivers filled out an adapted version of the Informant Questionnaire on Cognitive Functioning in the Elderly (IQ-CODE-N). Cognitive impairments were reported by approximately one quarter of patients.

Liu (2021) evaluated the Telephone Interview of Cognitive Status-40 (TICS-40 almost identical to TICS-M) in elderly post-COVID-19 patients 6 months after COVID-19?. They found no differences in TICS-40 score between COVID-19 patients with non-severe acute phase and controls after an average follow-up of 6 months (median both 24, IQR 18 to 28). COVID-19 patients who suffered a severe acute phase, had significantly lower TICS-40 scores (median 30, IQR 26 to 33, $p < 0.001$).

Zoeken en selecteren

Clinical question

Is a (repeated) cognition screening (I) recommended in patients with ongoing symptoms of cognitive difficulties (brain fog, i.e. difficulties with concentration, memory, language and/or executive function) ≥ 4 weeks after COVID-19 (P) in primary care?

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 28-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies answering the clinical question were selected. The Appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion. The search was updated on August 31st 2021.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Referenties

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Prevalentie nieuwe aandoeningen na COVID-19

Uitgangsvraag

Wat is de prevalentie van aandoeningen als longembolie, myocarditis, pericarditis, dementie, myocardinfarct, depressie en PTSS bij patiënten die COVID-19 (≥ 3 maanden geleden) hebben doorgemaakt in vergelijking tot patiënten die nooit COVID-19 hebben doorgemaakt?

Aanbeveling

De incidentie van specifieke andere aandoeningen > 3 maanden na COVID-19 lijkt niet verhoogd ten opzichte van patiënten die geen COVID-19 door hebben gemaakt.

De resultaten uit de literatuursamenvatting leiden niet tot specifieke aanbevelingen over aanvullend onderzoek, controles, of verwijzing.

Onderbouwing

Achtergrond

Er zijn aanwijzingen dat de incidentie van bijvoorbeeld cardiovasculaire events verhoogd is bij de groep patiënten die COVID-19 doormaakten. In deze module beschrijven we wat er bekend is over de prevalentie van de meest belangrijke aandoeningen bij patiënten na een SARS-CoV-2-infectie. Hierbij keken we vooral (maar niet uitsluitend) naar longembolie, myocarditis, pericarditis, dementie, myocardinfarct, depressie en posttraumatische stressstoornis (PTSS).

Conclusies / Summary of Findings

- Gehospitaliseerde -patiënten met doorgemaakte COVID-19 hebben mogelijk een hogere kans op morbiditeit (respiratoire aandoeningen, diabetes, cardiovasculaire aandoeningen, chronische nier- en/of leverschade) ten opzichte van patiënten die geen COVID-19 doormaakten (kwaliteit van bewijs: laag).
- We zijn onzeker of patiënten met doorgemaakte COVID-19 een verhoogde kans hebben op psychiatrische stoornissen, zoals PTSS, depressie of psychose (kwaliteit van bewijs: zeer laag).
- Er zijn geen onderzoeken van voldoende kwaliteit om iets te kunnen zeggen over de prevalentie van specifieke andere aandoeningen na COVID-19.
- Bovenstaande resultaten leiden niet tot specifieke aanbevelingen over aanvullend onderzoek, controles of verwijzing.

Samenvatting literatuur

The search yielded 381 unique references. Of these, 6 were included for review. In addition 1 references were included that were identified outside the search.

General

Ayoubkhani (UK, 2021): This matched, retrospective cohort study included 47780 hospitalized COVID-19 patients (mean age 65 years, 55% male), and matched these in a 1:1 ratio to the general population based on a large set of confounding variables, using electronic health records from the last 10 years. Mean follow-up

was 140 days. Most important results are 7.7 times greater death rate in post-COVID-19 group (320 [312-328] vs 41 [39-44] per 1000 person years), higher rates of respiratory diseases (6 times more often in total, and up to 27 times when only counting new respiratory diagnoses), but also higher rates of diabetes, chronic kidney / liver disease and major adverse cardiovascular events.

Respiratory disease was diagnosed in 14 140 individuals (29.6%) after discharge, with 6085 of these being new onset diagnoses; the resulting rates of 770 (95% confidence interval 758 to 783) and 539 (525 to 553) per 1000 person years, respectively, were 6.0 (5.7 to 6.2) and 27.3 (24.0 to 31.2) times greater than those in controls.

Psychiatric diseases

Non-western studies;

Oh (South Korea, 2021): population-based cohort study (n=129,120 patients, of whom 8,070 post-COVID-19 patients), based on health record screening, investigating new diagnoses of depression, psychosis, drug/alcohol abuse. No timing after COVID-19 mentioned. Incidence post-COVID-19 for depression 4.9 vs 1.0%. Incidence post-COVID-19 for psychosis 0.2 vs 0.0% and alcohol abuse (0.4 vs 0.2%). Drug abuse incidence was 0.0% in both groups (NS). After accounting for competing events / confounders, incidence of depression and psychosis remained significantly higher post-COVID-19. ORs 3.3 for depression, 2.5 for psychosis. (3.0 in total for psychological sequelae)

Chang (South Korea, 2020): 107 post hospitalized COVID-19 patients, FU average ~107 days after hospital admission. All were called, 64 were reached for phone interview, where a self-report screening tool was used; 13 (20.3%) had PTSD based on this. The tool used (Post-traumatic Stress Disorder Checklist-5), normally is only used for assessment of PTS symptoms, not for confirming a diagnosis.

Simani (Iran, 2021): assessment of PTSD and/or CFS/ME (chronic fatigue syndrome/myalgic encephalomyelitis). N=120 (out of 240 eligible), questionnaires 6 months after hospitalization; CFS prevalence 17.5%, PTSD 5.8%.

Western studies;

Tarsitani (Italy, 2021): N=115 post-hospitalized patients (but 77% non-critical disease), FU 3 months after discharge. PTSD was present in 12 (10.4%) of the patients. 2 of these had been hospitalized on ICU.

- Einvik (Norway, 2021): N=583, 125 hospitalized, 458 non hospitalized. FU 1.5-6 months after infection. PTSD was present in 11 (9.5%) of hospitalized and 32 (7.0%) of non-hospitalized patients. 8.6% in women, 6.3% in men. Being born outside of Norway was associated with PTSD (so hospitalization was not).

Cardiovascular diseases

No separate studies on cardiovascular events only.

Pulmonary

Rogliani (Italy, 2020): Very small study investigating changes in high resolution CT scan (HRCT), looking for pulmonary fibrosis. 27 out of 109 hospitalized subjects were included, as they had a follow-up HRCT (bias).

Disease severity was mostly mild to moderate. All pulmonary opacities had resolved at follow-up (average 47 days after discharge). None had pulmonary fibrosis.

Kwaliteit van bewijs

Het onderzoek van Ayoubkhani (2021) is van lage kwaliteit. De andere beschreven onderzoeken zijn van zeer lage kwaliteit, met name vanwege het ontbreken van een controlegroep. Daarnaast speelt bij niet-Westerse onderzoeken naar psychologische/psychiatrische sequelae het probleem van generaliseerbaarheid naar de Nederlandse situatie, gezien de grote cultuurverschillen en normen en waarden ten aanzien van de omgang met ziekte en tegenslag.

Zoeken en selecteren

Op 18-06-2021 is een literatuurzoekactie naar systematische reviews, randomized controlled trials (RCT's) en observationeel onderzoek uitgevoerd in PubMed en Embase. Voor deze vraag is gezocht met de elementen post-acute covid (P), specifieke aandoeningen en prevalentie/epidemiologie. Studies werden geselecteerd op basis van full-tekst, gebaseerd op de criteria zoals genoemd in de uitgangsvraag.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Startpagina - Follow-up, diagnostiek en multidisciplinair overleg in de tweede lijn bij COVID-19

Waar gaan deze richtlijnmodules over?

In deze modules (in herziening) komen de volgende onderwerpen aan bod:

- de waarde en plaats van inspanningsdiagnostiek
- de waarde van de CT Thorax
- de waarde van cardiale MRI
- de inzet van meetinstrumenten in de tweede lijn
- de waarde van MRI Hersenen
- de waarde en plaats van het multidisciplinair diagnostisch overleg

Voor wie zijn deze richtlijnmodules bedoeld?

Deze richtlijn is in eerste instantie bedoeld voor alle zorgprofessionals in de tweede lijn die betrokken zijn bij de zorg aan patiënten met langdurige klachten na COVID-19. In de verantwoording van elke module staat beschreven welke verenigingen en organisaties de desbetreffende module hebben geautoriseerd of geacordeerd.

In deze richtlijn maken we geen onderscheid tussen de tweede en derde lijn.

Voor patiënten

Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over COVID-19. Daarnaast is aanvullende informatie beschikbaar op het [Coronaplein](https://coronaplein.nl) en [C-support.nu](https://c-support.nu).

Hoe zijn deze richtlijnmodules tot stand gekomen?

Deze modules zijn ontwikkeld binnen het project 'Richtlijn Langdurige klachten na COVID-19'. In de verantwoording worden het ontwikkelproces en de samenstelling van de stuur-, werk- en klankbordgroep in detail beschreven.

Toepassing

Bij deze richtlijnmodules zijn een e-learning module en een webinar ontwikkeld. De e-learning is bedoeld voor medisch specialisten (met name longartsen, klinisch geriaters, internisten en revalidatieartsen) en huisartsen en is op elk gewenst moment te starten. Deze is geaccrediteerd met 2 punten (ABAN). Op 2 juni 2022 vond een webinar plaats, waarin drie thema's uit de richtlijn worden uitgelicht met specifieke ervaringen en uitdagingen uit de praktijk. [Kijk deze hier terug](#), gebruik het wachtwoord 0a5W%pyi.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Inspanningsdiagnostiek na COVID-19

Uitgangsvraag

Wat is de waarde en/of plaats van inspanningsdiagnostiek (CPET) in de nazorg voor patiënten met aanhoudende klachten na COVID-19?

Aanbeveling

Overweeg in overleg met de patiënt de inzet van inspanningsdiagnostiek met ademgasanalyse (CPET) indien er na COVID-19 sprake is van ≥ 1 van de volgende factoren:

- onduidelijkheid over de veiligheid van fysieke inspanning door comorbiditeit op de voor beweging cruciale orgaansystemen (hart/long en/of bewegingsapparaat)
- stagnerend herstel van de fysieke fitheid ≥ 3 maanden, ondanks begeleiding (fysio-/oefentherapie, ergotherapie, diëtetiek en eventueel logopedie) in de eerste lijn
- aanhoudende klachten van vermoeidheid, kortademigheid, aspecifieke thoracale klachten, verminderde inspanningstolerantie of bewegingsangst ≥ 3 maanden, ondanks begeleiding (fysio-/oefentherapie, ergotherapie, diëtetiek en eventueel logopedie) in de eerste lijn

Overwegingen

Voor- en nadelen van de interventie

Er zijn geen gerandomiseerde onderzoeken gevonden die de waarde van inspanningsdiagnostiek met ademgasanalyse (cardiopulmonary exercise testing; CPET) bij COVID-19 patiënten hebben onderzocht. De huidige observationele onderzoeken zijn veelal beschrijvend van aard en laten over het algemeen zien dat het uithoudingsvermogen ook behoorlijke tijd (tot 6 maanden) na COVID-19 verminderd kan zijn. Er zijn zeer voorzichtige aanwijzingen in het literatuuronderzoek dat er bij een gedeelte van de patiënten sprake is van ventilatoire inefficiëntie en dat er een mogelijke samenhang is tussen dyspneu en de verminderde fitheid. Weinig onderzoeken verschaffen duidelijkheid over de diagnostische opbrengst van de CPET, dat wil zeggen dat men niet rapporteert in hoeverre de inzet van CPET heeft geresulteerd in een (andere) diagnose met behandelconsequentie. Wel is er sprake van cardiale, pulmonale, mitochondriële, ventilatoire en/of verminderde zuurstofopnamecapaciteit als duiding van de vermoeidheids- en dyspneuklachten. Ook wordt in meerdere onderzoeken aangegeven dat er een indicatie is voor een beweeginterventie. Het blijft vaak onduidelijk of de patiënten voorafgaand aan de CPET reeds aan trainingsprogramma's hadden deelgenomen.

CPET is een veilige vorm van diagnostiek waarbij meerdere orgaansystemen tegelijk doorgemeten worden tijdens een maximale inspanningstest. CPET biedt de mogelijkheid om cardiale, pulmonale en/of mitochondriële aandoeningen uit te sluiten (Wasserman, 2005; Levett, 2018; Mezzani, 2017), het probleem en/of beperking te benoemen en/of de patiënt gerust te stellen over onderliggende pathofysiologische bevindingen. Een bijkomend voordeel van CPET is het vrijkomen van diverse parameters over fysieke fitheid uitgedrukt in zuurstofopnamecapaciteit ($VO_2\text{max}$ en afgeleiden). Deze parameters vormen samen het patiëntspecifieke inspanningsfysiologische profiel; het geeft de behandelaar en patiënt inzicht over de individuele fysieke fitheid en tot op welk niveau veilig (denk aan saturatiedips, ritmeproblematiek, ischemie,

hypertensief bloeddrukverloop, bijwerkingen medicatie (bijvoorbeeld bètablokkers)) getraind kan worden. Op basis van dit profiel kan een gepersonaliseerde SMART (individueel bepaald en stapsgewijs in opbouw) beweeginterventie worden samengesteld.

Hiermee heeft CPET volgens de werkgroep de potentie om bij te dragen aan doelmatige en passende zorg bij complex fysieke vraagstukken en/of bij aanhoudende onbegrepen verminderde inspanningstolerantie post COVID-19. In hart-, long- en oncologische revalidatie wordt CPET al op die manier toegepast.

De werkgroep adviseert de inzet van CPET te overwegen en met de patiënt te bespreken, indien er na COVID-19 sprake is van ≥ 1 van de volgende factoren:

- onduidelijkheid over de veiligheid van fysieke inspanning door comorbiditeit op de voor bewegingen cruciale orgaansystemen (hart/long en/of bewegingsapparaat)
- stagnerend herstel van de fysieke fitheid ≥ 3 maanden, ondanks adequate begeleiding (fysio-/oefentherapie, ergotherapie, diëtetiek en eventueel logopedie) in de eerste lijn
- aanhoudende klachten van vermoeidheid, kortademigheid, aspecifieke thoracale klachten, verminderde inspanningstolerantie of bewegingsangst ≥ 3 maanden, ondanks adequate begeleiding (fysio-/oefentherapie, ergotherapie, diëtetiek en eventueel logopedie) in de eerste lijn

Kwaliteit van bewijs

De bewijskracht is zeer laag. Hier ligt een kennislacune. De aanbevelingen zijn daarom gebaseerd op aanvullende argumenten, waaronder expert opinie, waar mogelijk onderbouwd met (indirecte) literatuur.

Waarden en voorkeuren van patiënten

Er is geen literatuur bekend over de patiënttevredenheid specifiek gericht op CPET. Voor de patiënt is het van belang dat CPET kan bijdragen aan het tot stand komen van een gerichte diagnose, probleembenoeming en plan van aanpak, waarbij ook geruststelling een factor van betekenis is. Dit alles vermindert mogelijk het doorlopen van meerdere parallelle orgaanspecialistische verwijstrajecten en verbetert mogelijk de therapietrouw voor het voorgestelde behandelplan. Tevens blijkt de CPET verhelderend te zijn voor de patiënt als het onderliggende probleem met name blijkt te liggen op het gebied van gebrek aan fysieke fitheid en/of leefstijl. CPET is een veilige en weinig belastende vorm van diagnostiek. Wel ervaren sommige patiënten het als zeer intensief. Dit dient te worden besproken met de patiënt. Dit hangt mogelijk deels samen met de timing. Voorwaarde voor het uitvoeren van een CPET is dat een patiënt minimaal zelfstandig kan fietsen op een hometrainer.

Verder noemen patiënten als nadeel nog wel eens de meting met het mondkapje. Sommige patiënten vinden dat een beangstigend onderdeel, maar in de praktijk is dit na een goede uitleg en coaching tijdens de test in de 1-op-1-setting van testende dokter en patiënt goed te overkomen. Het eventuele gebruik van een arteriële lijn kan bij een zeer klein percentage patiënten leiden tot complicaties.

Kosten

De kosten voor het uitvoeren van CPET bij patiënten met aanhoudende klachten na COVID-19 vallen onder de verzekerde zorg, als de interventie voldoet aan de criteria voor verzekerde zorg. De kosten zijn € 550-800

per DBC (inclusief alle contacten) met een looptijd van 3-4 maanden. Hoewel kosteneffectiviteitsdata ontbreken, bespaart CPET mogelijk verdere zorgkosten doordat het mogelijk verdere orgaanspecifieke verwijzingen voorkomt (Blokland, 2020). De COFIT-studie die op dit moment in Nederland wordt uitgevoerd kan daar in de nabije toekomst meer inzicht in geven.

Aanvaardbaarheid

De werkgroep is van mening dat de inzet van CPET volgens scherpe, doelmatige indicatiecriteria moet plaatsvinden, en dat de inzet van CPET van meerwaarde kan zijn als geïntegreerd cardiopulmonaal en tevens mitochondrieel/inspanningsfysiologisch diagnosticum bij patiënten met langdurige, aanhoudende en onbegrepen klachten post COVID-19.

Haalbaarheid

CPET-diagnostiek vergt expertise van inspanningspathofysiologie en prescriptie van beweeginterventie in combinatie met competenties met betrekking tot interne geneeskunde, (sport)cardiologie en pulmonologie (Neunhaeuser, 2021). CPET is in Nederland regionaal goed verspreid aanwezig, laagdrempelig beschikbaar en toegankelijk. De werkgroep verwacht daarom geen barrières op het gebied van haalbaarheid en implementatie van de huidige richtlijn.

CPET wordt in de medische praktijk echter nog relatief weinig toegepast als diagnosticum in de hoedanigheid van 'interactieve geïntegreerde orgaansysteem meting'.

Waarom deze aanbeveling/rationale?

Een aanzienlijke groep patiënten heeft 3 maanden na doorgemaakte COVID-19 nog aanhoudende onbegrepen klachten, die dagelijks leven, werk en of gezond bewegen in de weg staan.

De werkgroep is op basis van de uitkomsten van het literatuuronderzoek, de mogelijkheden die de CPET biedt bij een veilige en relatief lage belasting voor de patiënt en vanuit het patiëntperspectief van mening dat de inzet van de CPET van meerwaarde kan zijn bij bepaalde patiënten. Met CPET kan in relatief korte tijd simultane diagnostiek verricht worden op 3 orgaansystemen. Ook kan de patiënt op basis van CPET op basis van het inspanningsfysiologische profiel (inspanningscapaciteit) gepersonaliseerd SMART en goedkoop/zelfstandig trainen. Hierdoor worden mogelijk verdere zorgkosten bespaard door het voorkomen van verdere orgaanspecifieke verwijzingen. Om deze redenen raadt de werkgroep aan om de optie voor een CPET te overwegen en met de patiënt te bespreken.

Onderbouwing

Achtergrond

Een aanzienlijke groep patiënten ervaart 3 maanden na doorgemaakte COVID-19 aanhoudende onbegrepen klachten (zie de module Natuurlijk beloop). Meerdere onderzoeken (Arnold, 2021; Raman, 2021; Goërtz, 2020) laten zien dat vermoeidheidsklachten, dyspneu, myalgie en pijn op de borst de meest voorkomende klachten zijn (zie de module Natuurlijk beloop).

Pathofysiologisch zijn deze klachten niet eenvoudig te duiden door basaal lichamelijk en aanvullend onderzoek (x-thorax, ecg en longfunctie). Ook is er veelal sprake van gedeeltelijk of volledig natuurlijk herstel van gevonden cardiale en/of pulmonale afwijkingen (Zhou, 2020; Van der Borst, 2020). De beschreven

klachten zijn mogelijk een uiting van conditioneel onvermogen/een slechte fysieke fitheid, die meetbaar is als verlaagde zuurstofopnamecapaciteit ($VO_2\text{max}$).

Inspanningsdiagnostiek met ademgasanalyse (CardioPulmonary Exercise Testing; CPET) levert geïntegreerde data over de gelijktijdig optredende en interactieve cardiovasculaire, ventilatoire (inclusief gaswisseling), metabole en musculoskeletale (mitochondriën) respons op fysieke inspanning (Mezzani, 2017; Wasserman, 2005). CPET geeft daarmee de mogelijkheid om middels 1 test differentiaaldiagnostisch onderscheid te maken tussen cardiale, pulmonale en mitochondriële factoren en/of een gebrek aan conditionele fysieke fitheid (Wasserman, 2005; Ross, 2016; Blokland, 2020) als origine van de klachten. Het heeft daarmee potentie als doelmatig medisch-specialistisch diagnosticum. Er is geen enkel ander diagnosticum dat deze combinatie van diagnostische eigenschappen in zich heeft (Liu, 2021; Wasserman, 2005). De meerwaarde van CPET bij patiënten met aanhoudende klachten na COVID-19 is echter nog onduidelijk.

Conclusies / Summary of Findings

PICO 1:

It is unclear whether post-acute care including the use of CPET affects cardiopulmonary symptoms/diagnoses, cardiorespiratory fitness, exercise tolerance, fears about exercise, quality of life, and patient satisfaction compared to post-acute care without the use of CPET in patients with persisting complaints after COVID-19.

PICO 2:

There was some variation in the patient populations among studies. In general, the literature suggests that in a substantial part of the patients after COVID-19 exercise tolerance seems to be reduced, and there are some indications for ventilatory inefficiency (e.g. ventilation/perfusion mismatch or gas exchange problems). Most studies did not report on cardiopulmonary symptoms with a consequence for treatment, or requiring an intervention/medication. However, the study of Kersten (2021) indicated that cardiopulmonary symptoms might be present in a selected population, and that CPET might be useful to identify these symptoms. Given the nature of the studies, however, the results should be interpreted with caution.

Samenvatting literatuur

No studies were included in the analysis of the literature. A descriptive summary of CPET findings (PICO 2) from 4 studies published before May 4, and 8 studies published between May and September 7, is presented in table 1. Due to the explorative nature of the data, the evidence could not be graded.

Table 1. CPET results and patient experience

Reference	CPET timing method	Study population	VO ₂ peak (ml/kg/min) %VO ₂ peak predicted Wmax (W)	VO ₂ AT (ml/kg/min or ml/min)	VE/VCO ₂ slope	RER	HR peak (bpm) % predic
	181 (42)			13.6 (9.2;17)			

Aparisi, (2021) n=70 Spain	days after hospital discharge.	With dyspnea (NYHA functional class $\geq$ II; (n=41).	17.8 (15.8;21.2)		32 (28.1;37.4)	1.08 (1.05;1.116)	148 (140;159)
	Treadmill.	Needed hospitalization: 78% % female: 73.2 Age: 54.9 (10.5) BMI: 28 (4.9)	77.8 (64;92.5)				87 (79.3;94.
		Without dyspnea (n=23).	22.8 (18.8;27.7)	18.3 (15.2;19.5)	29.4 (26.9;31.4)	1.13 (1.05;1.28)	161 (147;169)
		Needed hospitalization: 69% % female: 51.7 Age: 54.6 (13.9) BMI: 26 (3.9)	99 (88;105)				95 (88;105)

Barbagelata (2021) n=200 Argentinië mean (SD)	45-120 days after infection, mean 80 (21) days. Treadmill.	With 'post-covid syndrome': dyspnea (>1 mMRC) or fatigue (>4 VAS) persisting for ≥days after symptom onset (n=112). Needed hospitalization: 19.6% % female: 58.9 Age: 47.9 ± 13.4 BMI: 26.3 ± 6.8	25.8 (8.1) 89.7 (19.9)	NR	33.1 (5.9)	NR (52.7% had a RER >1.1)	NR

		without 'post-covid syndrome' (n=88). Needed hospitalization: 19.3% % female: 41.1 Age: 50.0 ± 15.4 BMI: 26.6 ± 5.8 This group had a higher proportion of subjects with previous cardiovascular disease.	28.8 (9.6) 92.9 (18.7)	NR	32.5 (5.5)	NR (68.2% had a RER >1.1)	NR
Clavario (2021) n=200 Italy	Three months after hospital discharge. Cycle ergometer.	Needed hospitalization: 100% % female: 43 Age: 58.8 (51;66.0) BMI: 26.6 (24.1;30.2) Dyspnea: 59% NYHA Class III/IV: 27% Chest pain: 31.5% fatigue: 57.5%	20.1 (16.5;24.4) 85.0 (74.0;98.2) 121.5 (91.8;165.2)	1019.5 (822.0;1283.8)	NR	1.1 (1.1;1.2)	149.0 (133.8;164.2) 91.9 (82.2;98.6)

Debeaumont (2021) n=23 France	Six months after hospital discharge. Cycle ergometer.	Patients with persistent symptoms (fatigue or dyspnea) following hospitalization. % female: 48 Age: 59 (13) BMI: 29 (4)	19.0 (6.8) 84 (19)% 125 (54) Wmax (%): 90 (24)	NR	32 (5)	1.14 (0.15)	143 (25) 85 (12)
Dorelli (2021) n= 28 Italy -	More than 5 months after hospital discharge, mean 169 (28) days. Cycle ergometer.	Needed hospitalization: 100% % female: 21 Age: 55.3 (52.3;61.0=9) BMI: 25.9 (3.4) Patiënts >65 years, with concomitant previous respiratory or non-respiratory diseases (except for stable arterial hypertension) and BMI ≥ 35 years were excluded.	29.2 (8.3) NR 187.7 (64)	17.6 (IQR=15.9;22.4)	27.7 (3.9)	1.19 (1.11;1.25)	156.6 (18)

Kersten, 2021 n = 36 Germany	Median (SD) 122 (77) days after acute illness. Treatmill.	231 Patients referred to a long COVID unit for the diagnosis of potential post- inflammatory organ damage. Based on the results of laboratory tests, 12-lead ECG, transthoracic echocardiography, body plethysmography, capillary blood gas test and 6-min walk test, 36 patients had further diagnostics, including CPET.	NR	NR	NR	NR	NR

Liu (2021) n=41 China The same patients might have been included in Liu (2021) and Xiao (2021)	Seven months after hospital discharge. Treadmill.	Fibrosis (n=12). Needed hospitalization: 100% % female: 42 Age: 63 (12) BMI: NR	16.4 (3.6)	14.6 (3.7):	30.6 (4.0)	<u>NR</u>	<u>NR</u>
		Non-fibrosis (n=27). Needed hospitalization: 100% % female: 48 Age: 45 (11) BMI: NR	20.2 (3.7)	16 (3.5)	26.3 (3.2)	NR	NR
Liu (2021) [2] n=37 China The same patients might have been included in Liu (2021) and Xiao (2021).	Six months after hospital discharge. Treadmill.	Needed hospitalization: 100% % female: 50 Age: 50.5 (41.3;57.0) BMI: NR	19.1 (4.1)	15.8 (3.5)	27.4 (3.9)	NR	NR

Raman (2021) n=58 United Kingdom	Two-tree months after hospital discharge (median 1.6 months from discharge). Cycle ergometer.	Needed hospitalization: 100% % female: 41.4 Age: 55.4 (13.2) BMI: 30.8 (26.2;36.4)	80.5 (23.1) <80%: 54.9%	NR (AT - % of predicted VO2max: 40.7 (IQR 36.2;47.5))	33.4 (IQR=29.2; 40.3)	NR	NR
Rinaldo (2021) n=70 Italy	Mean 97 (26) days in follow-up. Cycle ergometer.	Mild-moderate disease (WHO criteria) during hospital admission (n=18). % female:50 Age: 50 (9) BMI: 26.7 (5.3)	22.1 (6.3) 83 (17) Wpeak predicted: 84 (14)	NR (AT % VO2 max predicted: 52 (14))	27.1 (2.6)	1.22 (0.09)	NR (%HRR: 1 (13))

		Severe disease (WHO criteria) during hospital admission (n=18). % female:61 Age: 58 (13) BMI: 28.2 (4.4)	18.4 (5.0) 82 (16) Wpeak predicted: 88 (29)	NR (AT % VO2 max predicted: 56 (15))	29.8 (3.9)	1.18 (0.11)	NR (%HRR: 16(13))
		Critical disease (WHO criteria) during hospital admission (n=39). % female:31 Age: 59 (11) BMI: 29.6 (4.2)	19.8 (5.1) 84 (15) Wpeak predicted: 85 (15)	NR (AT % VO2 max predicted: 55 (12))	28.3 (2.6)	1.21 (0.1)	NR (%HRR: 12(10))
Skjorten (2021) n=157 Norway	Three months after hospital discharge.	Dyspnea (mMRC 1-4) (n=59).	23.6 (7.9) 76 (16)	1376 (348) 1436 (469)	28.9 (4.5)	1.05 (0.09)	152 (18) 89 (9)
	Patients with pre-existing cardiovascular disease or COPD were excluded.	Needed hospitalization: 100% % female: 33 Age: 55.1 (10.6) BMI: 28.9 (4.8)					
	Treadmill.	No Dyspnea (1-4) (n=67). Needed hospitalization: 100% % female: 33 Age: 54.6 (13.8) BMI: 27.2 (3.9)	31.9 (9.3) 89 (18)		26.6 (4.4)	1.08 (0.10)	162 (20) 94 (9)

Xiao (2021) n=35 China The same patients might have been included in Liu (2021) and Liu (2021)	Six months after hospital discharge. Cycle ergometer.	Demographics only provided for the whole group (n=56), not for the subgroup that participated in the CPET. Needed hospitalization: 100% % female: 50 Age: 48 (15) BMI: NR	VO2max >20: 40% 15-20: 45.7% 10-15: 14% % predicted peak VO2≥80%: yes: 17; no: 83	VO2AT >14: 80% 11-14: 11.4% 8-11: 8.6%	≤30% yes: 77.1 no: 22.9	NR	NR

Data are mean (Standard deviation) or median (interquartile range). CPET: cardiopulmonary exercise test, VO₂: peak oxygen consumption, VO₂AT: VO₂ at anaerobic threshold, HR peak: heart rate,, RER: respiratory exchange ratio, mMRC: modified Medical Research Counsel., WHO: World Health Organization.

Zoeken en selecteren

Clinical question

What is the value and/or place of cardiopulmonary exercise testing in post-acute care for patients with persisting complaints after COVID-19?

PICO 1

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of COVID-19)

I: Post-acute care including the use of cardiopulmonary exercise testing (CPET)

C: Post-acute care without the use of CPET

O: Cardiopulmonary symptoms/diagnoses, cardiorespiratory fitness, exercise tolerance

Fears about exercise, quality of life, patient satisfaction

Other selection criteria

Study design: systematic reviews, RCTs, observational studies

Follow-up: at least 6 weeks after COVID-19

Study population: at least 10 patients per study arm

PICO 2

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of COVID-19)

I: CPET

C: -

O: Cardiorespiratory fitness, cardiopulmonary symptoms with a consequence for treatment, or requiring an intervention/medication

Other selection criteria

Study design: systematic reviews, observational studies

Follow-up: at least 6 weeks after COVID-19

Study population: at least 20 patients per study

The working group considered it unlikely that intervention studies as indicated by PICO 1 are already published. In case no studies were found in line with PICO 1, the systematically searched literature would be used to describe findings by CPET, as indicated by PICO 2. This evidence cannot be graded.

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2019 up to and including May 4, 2021. The search was updated on September 7, 2012. The detailed search strategy is depicted under Methods (*Verantwoording*). No studies were found to support PICO 1. Studies published before May 4 were selected based on the criteria as described in PICO 2. Studies published between May 4 and September 7 were included only when (1) the results were divergent from the prior conclusions; (2) the results provided new insights; or (3) a very large patient population (>1000 patients) was included. The appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The cardiopulmonary symptoms were reviewed by the working group. The working group did not define the other outcomes a priori, but followed the definitions used in the studies.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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CT thorax na COVID-19

Uitgangsvraag

Wat is de waarde van een CT thorax in de nazorg van patiënten met aanhoudende pulmonale klachten na COVID-19?

Aanbeveling

Voer geen CT thorax uit bij COVID-19-patiënten met aanhoudende pulmonale klachten, tenzij andere diagnoses moeten worden uitgesloten.

Overwegingen

Voor- en nadelen van de interventie

Er is literatuuronderzoek verricht naar de voor- en nadelen van nazorg op basis van CT thorax bij patiënten met aanhoudende pulmonale klachten na COVID-19. Er zijn geen voordelen gevonden voor het standaard uitvoeren van een CT-scan. Nadelen kunnen zijn dat er longafwijkingen worden gevonden waarvan de (klinische) significantie onbekend is. Dit kan tot onrust leiden bij de patiënt en mogelijk tot onnodige follow-up CT-scans. Een ander nadeel kan zijn dat er ongewenste nevenbevindingen worden gevonden waarvan de klinische significantie onduidelijk is (bijvoorbeeld incidentalomen).

De prevalenties van gerapporteerde CT-afwijkingen tussen de onderzoeken varieert enorm. Dit komt mogelijk doordat er verschillen in de definities van de gerapporteerde afwijkingen bestaan of dat de gerapporteerde afwijkingen niet goed gespecificeerd zijn. De onderzoeken beschreven bij hoeveel patiënten een afwijking (bijvoorbeeld ground-glass opacity, GGO) voorkwam, maar niet de ernst van de afwijkingen. Niet in alle onderzoeken beoordeelden radiologische experts de CT-scans. Het is ook onduidelijk of de kwaliteit van de CT-scan mogelijk een rol speelt. Verschillen in het moment van het vervaardigen van een CT-scan kunnen grote gevolgen hebben voor de gevonden prevalentie van CT-afwijkingen. Hoe korter de follow-upduur, hoe meer afwijkingen aanwezig zullen zijn. Omgekeerd: hoe langer de follow-upduur, hoe waarschijnlijker het is dat afwijkingen resorberen.

Los van de heterogeniteit van de onderzoeken beschrijven maar 2 studies de relatie tussen de gevonden CT-afwijkingen en de ervaren klachten of kwaliteit van leven van de patiënt. Maar in 1 onderzoek wordt beschreven dat patiënten met aanhoudende benauwdheid meer CT-afwijkingen hebben. Meerdere onderzoeken beschrijven wel een mogelijke relatie tussen CT-afwijkingen op follow-up scans en een lagere longfunctie, maar het blijft onduidelijk wat de exacte relatie is met de (aanhoudende) klachten. Chen (2021) beschrijft dat afwijkingen op een CT-scan na een jaar geassocieerd zijn met een lage totale longcapaciteit (TLC) en restvolume (RV), hoewel de TLC en RV binnen de normaalwaarden vielen. Zhou (2021) vond vergelijkbare resultaten met een follow-up van 3 maanden. Johnsen (2021) vond een significante maar beperkte associatie tussen afwijkingen op de CT-scan en het FEV1. Ook Bardekci (2021) en Fria-Masson (2021) vonden een correlatie tussen afwijkingen op de CT-scan en FEV1. Van den Borst (2021) rapporteerde een afgenomen longdiffusiecapaciteit bij patiënten met pulmonale parenchymafwijkingen op de CT-scan na 3 maanden. Strumiliene (2021) en Orzes (2021) vonden ook een associatie tussen afwijkingen op de CT-scan en

een afgenomen diffusiecapaciteit. Yin (2021) vond een associatie tussen afwijkingen op de CT-scan na 3 maanden en aanhoudende dyspneu. Darcis (2021) vond daarentegen geen associatie tussen GGO na 3 maanden en aanhoudende klachten.

Hoewel er dus aanwijzingen zijn voor een relatie tussen afwijkingen op de CT-scan en een verminderde longfunctie, zijn de klinische relevantie en eventuele behandelconsequentie van gevonden afwijkingen op CT vooralsnog onduidelijk.

Kwaliteit van bewijs

Er zijn geen vergelijkende onderzoeken gevonden die de cruciale uitkomstmaten beschrijven. De kwaliteit van het bewijs is daarom zeer laag. Hier ligt een kennislacune. De heterogeniteit tussen de onderzoeken is hoog wat betreft de populatie, bijvoorbeeld van 7 tot 100% ernstige klachten. Slechts een deel van de onderzoeken is prospectief opgezet, waarbij de CT thorax na een aantal maanden wordt uitgevoerd bij alle patiënten uit het onderzoek. Daar kunnen echter ook patiënten zonder aanhoudende klachten tussen zitten.

Waarden en voorkeuren van patiënten

Sommige patiënten willen zelf graag een CT-scan om (ernstige) longafwijkingen uit te sluiten. Een CT-scan leidt mogelijk tot geruststelling indien er geen afwijkingen worden gevonden. Uit de literatuur blijkt echter ook dat in een deel van de onderzoeken hoge prevalenties van afwijkingen worden gevonden op de scan. Het zou dus ook juist tot ongewenste ongerustheid kunnen leiden bij patiënten, omdat onduidelijk is wat de waarde is van eventuele gevonden afwijkingen op de scan. Het is belangrijk om de voor- en nadelen van extra diagnostiek middels een CT thorax te bespreken met de patiënt.

Kosten

Indien bij alle patiënten met aanhoudende pulmonale klachten na COVID-19 standaard een CT thorax zou worden gemaakt, zouden de totale kosten hoog zijn, omdat het om hoge patiëntenaantallen gaat. De kosten voor het uitvoeren van een CT thorax in individuele gevallen zijn acceptabel.

Aanvaardbaarheid

Het is niet aanvaardbaar om standaard een CT thorax te maken bij patiënten met aanhoudende klachten, omdat er geen bewijs is dat dit het nazorgtraject kan beïnvloeden. Ook is er geen bewijs dat gevonden afwijkingen een relatie hebben met de klachten. In individuele gevallen kan in samenspraak met de patiënt of indien andere diagnoses moeten worden uitgesloten wel een CT-scan worden overwogen. Bij een vermoeden van een longembolie kan een CTA pulmonalis worden verricht. In andere gevallen juist een HRCT thorax zonder contrast.

Haalbaarheid

Het standaard uitvoeren van een CT thorax bij alle patiënten met aanhoudende pulmonale klachten na COVID-19 zou niet haalbaar zijn. In individuele gevallen is het wel haalbaar.

Waarom deze aanbeveling/rationale

Er zijn geen interventieonderzoeken verricht die bevindingen op de CT-scan hebben gebruikt om het nazorgtraject in te richten. Eén onderzoek vond een associatie tussen longafwijkingen op de scan en

benauwdheid. Het is daarbij onzeker wat de klinische relevantie en eventuele behandelconsequentie zijn van een licht lagere longfunctie bij patiënten met afwijkingen op de CT-scan. Daarnaast is er een grote variatie in het voorkomen van longafwijkingen tussen de verschillende onderzoeken, o.a. door verschillen in timing en de definitie van CT-afwijkingen. Het is onbekend of het uitvoeren van een CT-scan de patiënttevredenheid beïnvloedt. Het standaard uitvoeren van een CT thorax bij alle patiënten met aanhoudende pulmonale klachten na COVID-19 zou niet haalbaar zijn. Indien andere diagnoses moeten worden uitgesloten, kan wel een CT thorax worden overwogen. Bij een vermoeden van een longembolie kan een CTA pulmonalis worden verricht. In andere gevallen juist een HRCT thorax zonder contrast.

Onderbouwing

Achtergrond

Een deel van de patiënten met een doorgemaakte COVID-19-pneumonie blijft pulmonale klachten houden en/of ervaart vertraagd herstel (zie de module [Natuurlijk beloop](#)). Het is onduidelijk of een CT thorax (al dan niet met intraveneus contrastmiddel) pulmonale afwijkingen ten gevolge van een doorgemaakte COVID-19-pneumonie kan opsporen.

Conclusies / Summary of Findings

It is unclear whether post-acute care including the use of CT thorax affects patient satisfaction, quality of life or treatment consequences compared to post-acute care without the use of CT thorax for patients with persisting pulmonary complaints after COVID-19.

Samenvatting literatuur

No studies were included in the analysis of the literature. A descriptive summary of CT thorax findings (PICO 2) from one meta-analysis and nine additional observational studies published before May 4, is presented in tables 1 and 2. In the updated search, 20 additional studies were identified. Since the results were in line with the previous conclusions, they are not described in detail.

Due to the explorative nature of the data, the evidence could not be graded.

Description of studies

Important study characteristics are summarized in table 1.

Results

No intervention studies were found (PICO 1). A descriptive summary of CT findings (PICO 2) from 20 studies is presented in table 2. Study populations were heterogeneous and definitions for CT abnormalities varied or were not reported. In 20 studies, GGO appearance was reported in 12 to 86.9% of patients. In 11 studies, parenchymal band or fibrous stripe was reported in 11 to 69.2% of patients. In 10 studies, bronchovascular bundle distortion or bronchiectasis was found in 1.6 to 72% of patients. In 13 studies, consolidation was observed in 1.1 to 64% of patients. In 8 studies, interstitial thickening or interlobular septal thickening was reported in 0.8 to 80.7% of patients. Three studies reported CT score (0-25) and found mean scores from 2 to 7.2. Only one study reported TSS score (4.8 ± 3.9).

Only one study reported quality of life in association with CT findings. Differences in SF-12 scores were neither significant nor clinically relevant with 30.9 ± 1.7 in 31 patients with improved CT versus 31.3 ± 1.2 in 8 patients with no improvement on CT. Patient satisfaction was not reported in the included studies.

Due to the explorative nature of the data, the evidence could not be graded.

Table 1. Baseline characteristics of included studies

Study	Study design	Participants who completed follow-up (number, age, sex)	Severe cases	Comorbidities	Country
Liu, 2020	Retrospective	N=51 Age 46.6 ± 13.9 41.2% male	NA	Hypertension 13.7%; Diabetes mellitus 7.8%; Coronary heart disease 2%	China
Zhao, 2020	Retrospective	N= 55 Age 47.7 ± 15.5 58.2% male	7.3%	Hypertension 10.9%; Diabetes mellitus 3.6%; Cardiovascular disease 3.6%	China
Zhong, 2020	Retrospective	N=52 Age 45.5 ± 13.7 55.8% male	36.5%	Hypertension 23.1%; Diabetes mellitus 9.6%; Cardiac disease 5.8%; Cerebrovascular Disease 1.9%	China
Liang, 2020	Prospective	N=21 Age 41.3 ± 13.8 28% male	9.2%	Hypertension 6.6%; Cardiovascular disease 1.3%; Diabetes mellitus 3.9%; Thyroid disease 2.6%; Pulmonary tuberculosis 6.6%; Chronic bronchitis 3.9%; Asthma 2.6%	China
Tabatabaei, 2020	Retrospective	N=52 Age 50.2 ± 13.1 61.5% male	NA	Cardiac disease 11.5%; Diabetes mellitus 7.7%; Hypertension; 3.8%; Pulmonary disease 3.8%	Iran
Van den Borst, 2020	Prospective	N=84 Age 59 ± 14 60% male	37.1%	Cardiovascular disease 24%; Asthma 10%; COPD 6%; Hypertension 28%; Diabetes mellitus 14%; Chronic kidney disease 8%; Malignancy 20%; Immunocompromised status 15%	The Netherlands
Smet, 2021	Retrospective	N=220 Age 53 ± 13 61.4% male	100%	Hypertension 34.1%; Diabetes mellitus 17.7%	Belgium
Lerum, 2020	Prospective	N=103 Age 59 [49, 72] 52% male	14.6%	Hypertension 34.0%; Diabetes Mellitus 7.8%	Norway

Huang, 2019	"ambidirectional"	N=353 Age 57 [47, 65] 52% male	29.8%	Hypertension 29.1%; Diabetes Mellitus 11.9%; Cardiovascular disease 7.4%; Cerebrovascular disease 2.7%; Malignancy 2.5%; COPD 1.8%; Chronic Kidney Disease 1.6%	China
Guler, 2021	Prospective	N=52 Age 57.2 ± 12.1 59.3% male	58.4%	Hypertension 35.4%; Diabetes Mellitus 20.4%; Interstitial lung disease 4.4%; COPD 8.0%; Asthma 13.3%; GERD 9.7%; Sleep apnea 10.6%; Chronic heart failure 9.7%; Chronic Kidney Disease 11.5%; Malignancy 5.3%	Switzerland
Han, 2021	Prospective	N=114 Age 54 ± 12 70.2% male	NA	Hypertension 28.1%; Diabetes Mellitus 11.4%; Chronic pulmonary disease 14.0%	China
Zhang, 2021	Retrospective	N=122 Age 51 [31.8, 61.0] 49.7% male	26.5%	Emphysema 1%; Chronic bronchitis 1.6%; OTB 1.3%; Advanced ILD 0.6%; Hypertension 10.6%; Diabetes 3.5%; Coronary disease 2.6%	China
Gonzalez, 2021	Prospective	N=57 Age 60 [48, 65] 74.2% male	NA	Hypertension 37.1%; Diabetes mellitus 14.5%; Chronic heart disease 9.7%; Asthma 4.8%; COPD 4.8%	Spain
Parry, 2021	Retrospective	N=81 Age 51.8 ± 11.7 61.7% male	NA	Diabetes mellitus 17.3%; Hypertension 17.3%; COPD 11.1%; CKD 3.7%; CLD 3.7%; CAD 2.5%; Malignancy 2.5%; Immune suppression 1.2%	India
Froidure, 2021	Retrospective	N=107 Age 60 [53, 68] 59% male	100%	Overweight 63%; Documented respiratory condition 19%; Diabetes 22%; Hypertension 47%; Hypercholesterolemia 42%	Belgium
Morin, 2021	Prospective	N=170 Age 60.9 ± 16.1 57.9% male	NA	Hypertension 47.1%; Obesity 37.0%; Diabetes 26.8%; Chronic heart disease 16.1%; Respiratory disease (other than COPD) 15.7%; Chronic kidney disease 10.7%; Active cancer 3.8%; Other immunosuppression 3.8%	France
Liu, 2021	Prospective	N=41 Age 50 ± 14 54% male	37%	Diabetes 2%; Hypertension 7%; COPD 5%; Cardiovascular disease 2%; Hepatic disease 2%	China

Stylemans, 2021 (follow-up to Smet)	Retrospective	N=63 Age 56 [50, 64] 74% male	100%	Diabetes 15%; arterial hypertension 32%	Belgium
Gianella, 2021	Prospective	N=39 Age 62.5 [51, 71] 78% male	NA	Hypertension 28%; Diabetes 13%; Cardiovascular diseases 17.9%; Coronary heart disease 10%; Chronic respiratory diseases 21%; COPD 8%; Asthma 13%; Chronic kidney disease 8%; Malignancy 10%	Switzerland
Sonnweber, 2021	Prospective	N=145 Age 57±14 57% male	NA	Cardiovascular disease 40%; Hypertension 30%; Pulmonary disease 19%; Metabolic disease 43%; Chronic kidney disease 7%; Chronic liver disease 6%; Malignancy 12%; Immunodeficiency 6%	Austria

Table 2. CT abnormalities at follow-up

Study	Time of CT scan	GGO % (N)	Parenchymal band or fibrous stripe % (N)	Bronchovascular bundle distortion or bronchiectasis % (N)	Consolidation % (N)	Interstitial thickening or interlobular septal thickening % (N)	CT score (0-25)	TSS score
Liu, 2020	31 (20–37) days after discharge	33.3% (17)	NA	3.9% (2)	2.0% (1)	35.3% (18)	NR	NR
Zhao, 2020	64–93 days after Discharge	12.7% (7)	NA	NA	NA	27.3% (15)	NR	NR
Zhong, 2020	39.6 ± 6.0 days after symptom onset; 19.7 ± 4.1 days after discharge	63.5% (33)	36.5% (19)	7.7% (4)	9.6% (5)	5.8% (3)	NR	NR
Liang, 2020	3 months after discharge	23.8% (5)	NA	NA	NA	NA	NR	NR
Tabatabaei, 2020	91 ± 15.5 days after initial CT	36.5% (19)	19.2% (10)	NA	NA	NA	NR	NR

van den Borst, 2020	13.0 ± 2.2 weeks after symptom onset; 9.1 ± 1.6 weeks after discharge	86.9% (73)	64.3% (54)	60.7% (51)	NA	NA	NR	NR
Smet, 2021	74 ± 12 days after Diagnosis	25.0% (55)	NA	NA	3.6% (8)	NA	NR	NR
Lerum, 2020	83 [73, 90] days after hospital admission	23.3% (24)	18.4% (19)	NA	NA	NA	NR	NR
Huang, 2021	186 [175, 199] days after symptom onset	44.8% (158)	15.9% (56)	NA	1.1% (4)	0.8% (3)	NR	NR
Guler, 2021	128 [108, 144] days after symptom onset	57.7% (30)	51.9% (27)	38.5% (20)	28.8% (15)	1.9% (1)	NR	NR
Han, 2021	175 ± 20 days after symptom onset	62.3% (71)	NA	10.5% (12)	23.7% (27)	NA	NR	NR
Zhang, 2021	> 12 weeks after discharge (longest follow-up)	51.6% (63/122)	32% (39/122)	1.6% (2/122)	3.3% (4/122)	NA	NA	NA
Gonzalez, 2021	3 months after hospital discharge	59.6% (34/57)	NA	71.9% (41/57)	15.8% (9/57)	80.7% (46/57)	NA	4.8 ± 3.9
Parry, 2021	101.4 ± 9.8 days since first chest CT	20% (16/81)	11% (9/81)	7% (6/81)	12% (10/81)	5% (4/81)	NA	NA
Froidure, 2021	103 [85, 114] days after hospital admission	67% (73)	NA	NA	7% (8)	NA	NA	NA

Morin, 2021	4 months after hospitalization	42.4% (72/170)	19.4% (33/170)	NA	NA	NA	NA	NA
Liu, 2021	3 and 7 months after discharge	3m: 27% (11/41); 7m: 12% (5/41)	3m: 54% (22/41); 7m: 41% (17/41)	3m: 34% (14/41); 7m: 29% (12/41)	3m: 15% (6/41); 7m: 10% (4/41)	3m: 41% (17/41); 7m: 32% (13/41)	NA	NA
Stylemans, 2021	10 weeks and 6 months after COVID-19 pneumonia diagnosis	6m: 100% in 22 patients with CT score $\geq$ 5.	NA	NA	NA	NA	10w: 7 [4, 10]; 6m: 2 [0, 5]	NA
Gianella, 2021	3 months after admission	58% (23/39)	69.2% (27/39)	NA	2.6% (1/39)	NA	6.9 $\pm$ 5.0	NA
Sonnweber, 2021	60 and 100 days after COVID-19 diagnosis	60d: 70%; 100d: 52%	NA	60d: 32%; 100d: 6%	60d: 64%; 100d: 7%	NA	60d: 7.2 $\pm$ 0.6; 100d: 4.1 $\pm$ 0.7	NA

Values are shown as mean $\pm$ SD or median [Q1, Q3]. Abbreviations: CT computed tomography, GGO ground glass appearance, NA not applicable, NR not reported in systematic review. CORADS were not reported in the included studies.

Zoeken en selecteren

Clinical question

What is the value of CT thorax in post-acute care for patients with persisting pulmonary complaints after COVID-19?

PICO 1

P: Patients with persisting pulmonary complaints after COVID-19 ($\geq$ 4 weeks from onset of COVID-19)

I: Post-acute care including the use of CT thorax

C: Post-acute care without the use of CT thorax

O: Patient satisfaction, quality of life, treatment consequences (medication, number of interventions)

Other selection criteria

Study design: Systematic review, RCT and observational studies

Follow-up: at least 6 weeks after COVID-19

Study population: at least 10 patients per arm and 20 in the total study

PICO 2

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of acute COVID-19 illness)
I: CT thorax imaging
C: -
O: Treatment consequences (medication, number of interventions), frequency of CT abnormalities

Other selection criteria

Study design: RCT and observational studies

Follow-up: at least 6 weeks after COVID-19 infection

Study population: study population at least 20

The working group estimated that the probability that intervention studies as indicated by PICO 1 have not yet been published as high. In case no studies were found in line with PICO 1, the systematically searched literature would be used to describe findings by CT thorax, as indicated by PICO 2. This evidence cannot be graded.

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2019 up to and including May 4, 2021. The search was updated on September 7, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). No studies were found to support PICO 1. Studies were selected based on the criteria as described in PICO 2. Studies published between May 4 and September 9, 2021 were included only if (1) the results were divergent from the prior conclusions; (2) the results provided new insights; or (3) the study population was very large (>1000 patients). The appendices (*Bijlagen*) contain the [PRISMA flowchart](#) of the first as well as the updated search, showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group did not define the outcome measures a priori, but followed the definitions used in literature.

The following abnormalities on CT were considered relevant at follow-up: ground-glass opacity (GGO), parenchymal bands or fibrous stripes, consolidation (%), interstitial thickening or interlobular septal thickening, bronchovascular bundle distortion or bronchiectasis. Also severity and probability CT scoring methods like CT score, TSS score and CORADS were considered relevant.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Cardiale MRI na COVID-19

Uitgangsvraag

Wat is de waarde van cardiale MRI in de nazorg voor patiënten met aanhoudende cardiale klachten na COVID-19?

Aanbeveling

Verricht geen cardiale MRI bij patiënten na doorgemaakte COVID-19, tenzij er sprake is van specifieke cardiale klachten met een vermoeden van myocardschade (myocarditis), gesteund door een afwijkend ecg, afwijkende biomarkers of andere diagnostiek.

Overwegingen

Voor- en nadelen van de interventie

Het uitvoeren van een cardiale MRI (CMR) bij patiënten met aanhoudende cardiale of conditionele klachten na doorgemaakte COVID-19 wordt op dit moment niet standaard gedaan. Een recente state of the art paper (Petersen, 2021) stelt dat CMR overwogen kan worden wanneer het aannemelijk is dat het verrichten ervan klinische consequenties heeft of bij onverklaarde, aanhoudende of recidiverende cardiovasculaire symptomen (dyspneu, palpitaties, thoracale pijnklachten of hartfalen) als onderdeel van het 'systemic inflammatory post-COVID-19 syndroom' ≥ 4 weken na het doormaken van COVID-19.

Een voordeel om wel een CMR is mogelijk dat de CMR een relevante afwijking toont waardoor het behandelplan verandert. In de klinische praktijk wordt voorafgaand aan een CMR, naast het klachtenpatroon, ook de cardiale enzymen danwel de bevindingen op de ecg en hartecho meegewogen. CMR laat bij patiënten na doorgemaakte COVID-19 soms afwijkingen zien die klinische consequenties of relevantie kunnen hebben (Late Gadolinium Enhancement (LGE), afwijkende T1- en T2-waardes). CMR geldt als de gouden standaard om myocardschade vast te stellen binnen de algemene cardiologie. Een recent onderzoek onder relatief jonge patiënten toonde aan dat CMR 7 keer zo effectief is in het opsporen van aan COVID-19 gerelateerde myocardschade in vergelijking met de conventionele symptoomgeleide strategie en 3 keer zo effectief als een strategie gebaseerd op een combinatie van symptomen, ecg's, troponines en echocardiografie (Daniels, 2021). Dat komt vooral tot uiting in de LGE bij CMR. Deze is sterk geassocieerd met een slechte prognose bij patiënten met zowel actieve als herstelde myocarditiden. Daarnaast is de grootte en lokalisatie van LGE van additionele prognostische waarde. Dit geldt ook voor individuen met een (vooralsnog) normale ejectiefraction van de linkerventrikel. In het onderzoek van Peretto (2020) werden maligne kamerritmestoornissen gezien bij 30% van de patiënten gediagnosticeerd met myocarditis na 27 (± 7) maanden follow-up.

De relatie tussen klachten na doorgemaakte COVID-19 en afwijkende bevindingen op CMR is nog niet goed onderzocht. Er lopen een aantal grote prospectieve cohortonderzoeken naar de myocardiale schade bij patiënten met doorgemaakte COVID-19 en de meerwaarde van een cardiale MRI daarbij (onder andere de MaastricCht-cohort, COMMIT en CAPACITY-studie, die vallen onder het DEFENCE-consortium). In een retrospectief onderzoek (Huang, 2020) onder 26 patiënten met aanhoudende cardiale klachten (< 3 maanden) na doorgemaakte COVID-19, bleek 58% afwijkende CMR-bevindingen te hebben, zoals oedeem

(54%) en LGE (31%). In het onderzoek van Kravchenko (2021) werden 41 patiënten geïnccludeerd met aanhoudende cardiorespiratoire klachten na COVID-19 en 42 controlepatiënten zonder aanhoudende klachten. De mediane follow-upduur was 103 dagen. Er werd geen verschil gezien tussen beide groepen in CMR-afwijkingen en daarmee ook geen relatie met het klachtenpatroon. Opmerkelijk is de lage prevalentie van CMR-afwijkingen in dit onderzoek ten opzichte van de eerder verschenen CMR-onderzoeken na COVID-19. Dit kan te maken hebben met verschillend gehanteerde exclusiecriteria. In tegenstelling tot de meeste onderzoeken werden in het huidige onderzoek patiënten met pre-existente cardiopulmonaire ziektes geëxcludeerd en was de gemiddelde leeftijd beduidend lager. Kersten (2021) verrichtte een vergelijkbaar onderzoek. Van de 231 patiënten met aanhoudende cardiopulmonale klachten > 2 maanden sinds de acute infectie, werd bij 36 patiënten een CMR verricht. Bij 44,4% werden afwijkende CMR-bevindingen gevonden en bij > 50% geen afwijkingen op een CMR. Een belangrijke beperking van dit onderzoek is de selectiebias van patiënten die mogelijk verwezen werden op basis van de ernst van de klachten en dus geen cross-sectionele representatie is van patiënten met aanhoudende klachten na COVID-19. Breitbart (2021) liet een aanzienlijke lagere prevalentie zien van CMR-afwijkingen 2 maanden na infectie (14% en bij 2% (n = 1) myocarditis volgens de Lake Louis criteria).

Opvallend is dat de onderzoeken, los van aanhoudende klachten, grote verschillen laten zien in prevalentie van CMR-afwijkingen. Zo laat Puntmann (2021) bij driekwart van de patiënten na een milde infectie CMR-afwijkingen zien, terwijl Joy (2021) dat bij een kleine 10% bij 6 maanden na infectie laat zien. Bovendien liet een vergelijking met een gematchte controlegroep geen significant verschil zien.

Bij patiënten met aanhoudende thoracale klachten na doorgemaakte COVID-19 kan er sprake zijn van een andere diagnose die de klachten verklaart. Bij patiënten bij wie een andere diagnose in de differentiaaldiagnose staat, kan beeldvorming uiteraard wel geïndiceerd zijn.

Kwaliteit van het bewijs

Er is literatuuronderzoek gedaan naar de waarde van het inzetten van CMR bij aanhoudende cardiale klachten na COVID-19. Er zijn geen onderzoeken gevonden die behandeling op basis van CMR hebben beschreven. De huidige literatuur over myocardschade na COVID-19 geeft onvoldoende heldere antwoorden over de prevalentie, prognose en behandelmogelijkheden en de relatie met klachten, ecg-afwijkingen en verhoogde troponinwaarden. Op een enkele uitzondering na zijn de gepubliceerde onderzoeken klein (10-150 MRI-scans); ze zijn onderhevig aan sterke of juist niet beschreven selectie en er ontbreekt een gestructureerde follow-up en in het bijzonder adequate ritmemonitoring op langere termijn. De wisselende kwaliteit van de onderzoeken wordt weerspiegeld in de gerapporteerde prevalenties van myocardschade, die wisselen van 0-78%. (Friedrich, 2021). Doorgaans is een lagere onderzoekskwaliteit geassocieerd met zeer wisselende prevalenties.

Door het ontbreken van vergelijkende onderzoeken is de bewijskracht zeer laag. Hier ligt een kennislacune. De aanbevelingen worden daarom gebaseerd op aanvullende argumenten, waar mogelijk ondersteund met (indirect) bewijs, waaronder expert opinion. Er bestaat een grote behoefte aan prospectieve CMR-data in een goed omschreven populatie, met adequate follow-up op de lange termijn.

Waarden en voorkeuren van patiënten

Aanhoudende cardiale klachten na COVID-19 komen regelmatig voor en leiden tot een verminderde kwaliteit van leven (Carfi, 2020). Patiënten met deze klachten zullen hierdoor regelmatig verwezen worden naar de

cardioloog ter analyse en behandeling van deze klachten, waarbij er ook behoefte kan zijn aan aanvullend onderzoek om de klachten te objectiveren. Het uitvoeren van CMR kan echter resulteren in toevallsbevindingen, wat juist kan leiden tot een toename van onrust. Dit dient besproken te worden met de patiënt.

Kosten

De kosten van een CMR liggen tussen de € 250 en 400, afhankelijk van het ziekenhuis. Er kunnen aanvullende kosten ontstaan als er toevallsbevindingen worden gevonden, waarna verder aanvullend onderzoek nodig is, bijvoorbeeld aanvullende opnames of herhaling van de CMR na een bepaalde periode, en verdere risicostratificatie (zoals inspanningstesten en holters). Op basis van literatuuronderzoek en de conclusie van de werkgroep wordt de huidige praktijk niet veranderd en zijn er geen verschillen in kosten te verwachten.

Aanvaardbaarheid

Bij gebrek aan bewijs voor zinvolheid is er geen indicatie om standaard een CMR te verrichten. De kans op toevallsbevindingen kan leiden tot aanvullende (niet-zinnige) diagnostiek en dient tegen het licht gehouden te worden van de klinische relevante afwijkingen als ischemie of littekenvorming. Het verrichten van biochemisch, elektrofysiologisch en echografisch onderzoek voorafgaand aan de beslissing om wel of niet CMR te verrichten, kan de zinvolheid van CMR bij een selectie van patiënten vergroten.

Haalbaarheid

CMR wordt op dit moment niet standaard uitgevoerd. De werkgroep verwacht daarom geen barrières op het gebied van haalbaarheid en implementatie van de huidige richtlijn.

Waarom deze aanbeveling?

CMR bij patiënten na doorgemaakte COVID-19 laat afwijkingen zien met soms wel en soms weinig klinische betekenis. Er is geen goed vergelijkend onderzoek bekend tussen patiënten met en zonder cardiale klachten na doorgemaakte COVID-19 en de afwijkingen op CMR hierbij. Bij patiënten met aanhoudende cardiale klachten na COVID-19 is een standaard work-up aan te bevelen en een CMR wanneer conform de geldende richtlijnen hier op klinische gronden reden voor geacht wordt.

Onderbouwing

Achtergrond

Van de patiënten met doorgemaakte COVID-19, vertoont ongeveer 20% myocardiale schade (Shi, 2020; Guo, 2020) tijdens de actieve ziekte. Hierbij werd myocardiale schade in de meeste onderzoeken gedefinieerd als verhoogde troponinewaardes > 99^e percentiel. De aanwezigheid van verhoogde troponines is onafhankelijk geassocieerd met een verhoogde mortaliteit (HR 4,26; 95%-BI 1,92 tot 9,49) binnen enkele weken in deze populatie (Shi, 2020). In een geselecteerde populatie werden ≥ 3 maanden bij 78% van de patiënten met COVID-19 abnormale cardiale magnetic resonance (CMR) bevindingen gezien (gedefinieerd als afwijkend Late enhancement, T1- en T2-metingen). Bovendien had 60% tekenen van myocardiale inflammatie (Puntmann, 2020). In hoeverre deze afwijkingen na de infectie blijven bestaan, is nog onbekend. Het is de

vraag in hoeverre myocardiale inflammatie, aanwezige scar op MRI of verhoogde troponines na doorgemaakte COVID-19 gerelateerd zijn aan aanhoudende klachten, en of CMR een rol kan spelen in het vaststellen van schade die gerelateerd is aan de aanhoudende klachten na COVID-19.

Conclusies / Summary of Findings

PICO 1

It is unclear whether post-acute care including the use of CMR affects treatment consequences compared to post-acute care without the use of CMR in patients with persisting complaints after COVID-19.

PICO 2

The frequency of myocardial injury identified by CMR varies largely between studies, with insufficient information about treatment consequences for patients with persisting complaints after COVID-19.

Samenvatting literatuur

No studies were included in the analysis of the literature. A descriptive summary of CMR findings (PICO 2) is presented in table 1. Due to the limited yield of the first search, articles identified in the update were added. Due to the explorative nature of the data, the evidence could not be graded.

Table 1. Summary of included studies

Study	Study design	Population	Timing of imaging	Intervention/Imaging	Outcomes	Results

Breitbart, 2021	Observational study	N=56 Age 45.7 ± 12.2 46% male Hospital treatment 8.9%; Acute COVID-19 severity score 4.7 ± 2.2	Patients were included 71 $\pm$ 66 days after COVID-19	All patients underwent the CMR examination on a 1,5 Tesla scanner. Every scan was performed and evaluated jointly by a cardiologist and a radiologist, each certified as having the maximum level of qualification in cardiac MRI from their societies (German Cardiac Society, German Radiological Society). In a standardized protocol, the localizers were followed by evaluation of left ventricular function parameters using a semi-automatic approach.	Myocarditis, according to the 2018 Lake Louis criteria (myocarditis is diagnosed if both of the main criteria are positive: proof of (1) myocardial edema (T2 mapping or T2 darkblood TIRM-Sequences) and (2) non-ischemic myocardial injury (abnormal T1, ECV or LGE)).	Based on CMR findings, final diagnosis myocarditis was infrequent and confirmed in one out of 56 patients (2%). LGE 12.5 T1 values 1016.0 ± 28.2 T2 values 46.9 ± 3.1

Drakos, 2021	Single-center, retrospective, observational study	N=22 Age 51 (IQR 45–59) 64% male We did not include severely diseased COVID-19 patients with critical illness and/or acute respiratory distress syndrome (ARDS) during the acute phase. Patients with persisting symptoms of exertional dyspnoea (NYHA class II or III) and presence of fatigue suggestive of post-viral fatigue syndrome (PVFS) were included.	1-6 months after infection	CMR imaging was performed on a 1.5-T system during breath-hold and with ECG-triggering. The CMR protocol comprised cine-imaging, myocardial stress-perfusion and LGE-imaging, approximately 10–15 min after a cumulative gadolinium (Gadobutrol) dose of 0.15 mmol/kg. In addition, through-plane velocity-encoded (VENC) coronary sinus (CS) flow measurements with a pre-defined VENC factor of 100 cm/s (reflecting the maximum resolvable flow velocity and with adoption as needed) were performed at rest and approximately 1 min after regadenoson administration at maximal vasodilation.	Conventional CMR parameters, coronary sinus flow, global myocardial perfusion reserve	LGE presence 18% (non ischemic) LGE extent 0%

Joy, 2021	Prospective Case-Control study	N=74 Age 39 (30–48) 38% male COVID-19 severity: 15% asymptomatic; 24% noncase definition; 45% case definition; 1 person hospitalized. Case definition: one symptom or more of fever, cough, shortness of breath, anosmia, ageusia, dysgeusia.	Patients were included 6 months after infection	Scans were acquired at 2 sites: Royal Free (1 scanner) or Barts (2 scanners) between September 3, 2020, and November 7, 2020, in accordance with infection control guidelines on 1.5-T CMR scanners. Given pandemic pressures, an adapted 30-min protocol was used. This comprised anatomic images, long- and short-axis cines, T1, T2, and extracellular volume fraction (ECV) mapping (a mid-short axis and 4-chamber view each) with LGE and aortic pulse wave velocity. T1 mapping used a modified Look-Locker inversion recovery sequence (5s[3s]3s pre-contrast, 4s[1s]3s[1s]2s post-contrast).	Prevalence of myocarditis.	Prevalence of myocarditis-like scar was 4%.

Kersten, 2021	Single-center, prospective, observational study	N=36 Age 47.3 ± 14.2 50% Male COVID-19 severity: Asymptomatic 14.7%; Hospitalization 7.8%; Invasive ventilation 2.6%	All patients had a previous positive polymerase chain reaction (PCR) test for SARS-CoV-2 and had been released from quarantine at least 1 month previously	In Step 1, laboratory tests, a 12-lead electrocardiogram, transthoracic echocardiography, body plethysmography, a capillary blood gas test, and a 6-min walk test (6-MWT) were performed. Step 2 of the diagnostic workup consisted of cardiopulmonary exercise testing (CPET) and cardiovascular magnetic resonance imaging (CMR). The decision to proceed to Step 2 was made on the basis of all anamnestic and diagnostic data gathered in Step 1. CMR scans were obtained using a 1.5 T scanner under a standardized protocol in accordance with the guidelines of the Society for Cardiovascular Magnetic Resonance for the evaluation of inflammatory myocardial diseases. In Step 3, further diagnostics were performed on an individual basis.	We estimated cardiopulmonary sequelae in the meaning of real organ damage, such as myocarditis.	CMR showed (post-) inflammatory cardiac sequelae in 10 (27.8%) of the 36 patients, signs of myocarditis (such as nonischemic LGE or pathological findings in T2 mapping) in 9 cases and an unclear reduction of the left ventricular function in 1 patient.
	Retrospective	N=148	The interval	Cardiovascular	Functional	

Kotecha, 2021	multi-center observational study	Age 64 ± 12 70% male COVID-19 severity: Hospitalized 100%; ICU 32%. NB troponin elevation during admission was an inclusion criterium.	between discharge or confirmed diagnosis and CMR study was 56 days (IQR 30–88) and 68 days (IQR 39–103), respectively	magnetic resonance was performed in accordance with local institutional and international infection control guidelines on 1.5T CMR scanners. A standard CMR protocol including parametric mapping and post-contrast imaging. One-hundred and thirty-three patients underwent a full tissue characterization protocol (LGE, T1, and T2 mapping) including 76 with additional adenosine stress perfusion. Eleven patients underwent CMR without T1 and T2 mapping and four underwent a non-contrast CMR with T1 and T2 mapping.	metrics, multi-parametric myocardial mapping and LGE. When calculating ventricular volumes and mass, trabeculations and papillary muscles were included in the myocardial mass. Right ventricular insertion point LGE was not included as an abnormal LGE finding. The CMR diagnosis of myocarditis-like injury was made in accordance with published expert recommendations based on the presence of non-ischaemic myocardial injury in a typical distribution (patchy sub-epicardial or mid-wall LGE, which tends to favour the basal to mid inferolateral wall) and myocardial oedema (by T2 mapping). Active myocarditis was defined as the presence of non-	Myocardial infarction 22.3%; Myocardial infarction and ischaemic myocardial infarction 2.7%; Myocardial infarction and myocardial infarction 2.0%; Myocardial infarction 10.8%; Myocardial infarction and ischaemic myocardial infarction 4.7%; Non-ischaemic myocardial infarction 1.4%

					ischaemic myocarditis-pattern LGE with associated elevation in T1 and T2, or T2 alone, in the same distribution as LGE (i.e. T1 and T2 were measured within areas of LGE). Healed myocarditis was defined as the presence of nonischaemic myocarditis-pattern LGE with or without elevation in native T1 and with normal T2.

Kravchenko, 2021	Prospective observational study	N=41 Age 39 ± 13 43.9% male COVID-19 severity: Mild 90%; Moderate 10% Participants with cardiorespiratory chronic COVID-19 syndrome (CCS)		Each participant underwent a multiparametric cardiac MRI examination, which was performed using the same clinical whole-body MRI system (Ingenia 1.5T; Philips Healthcare, Best, The Netherlands). A 32-channel torso coil with a digital interface was used for signal reception. A signal intensity correction algorithm (constant level appearance; Philips Medical Systems) was used to correct for torso-coil related signal inhomogeneities. Electrocardiogram-gated steady state free-precession cine images were obtained in short-axis, two-chamber, and four-chamber views for functional analysis.	Signs of myocarditis.	None of the participants fulfilled the 2018 Lake Louise criteria for the diagnosis of myocarditis. Visible LC 7%; T1 relaxation time, native (ms) 978 ± 21 T2 relaxation time, native (ms) 53 ± 2

Li, 2021	Prospective, single-center, observational study	N=40 Age 54±12 60% male COVID-19 severity: Moderate 60%; Severe 40%; Admitted 100%	158 ± 18 days between hospital admission and cardiac MRI	Cardiac MRI were performed on a clinical 3T scanner (Skyra, Siemens Healthineers, Germany). For morphologic and functional analysis, steady-state free precession (SSFP) with breath-hold were performed, comprising a stack of contiguous parallel short-axis slices covering the entire left ventricle (LV) and right ventricle (RV) from base to apex and three LV long-axis slice (2-, 3-, and 4-chamber views) image was used for cardiac cine imaging with following parameters: field of view (FOV), 340-380 mm; repetition time (TR)/echo time (TE), 3.4/1.4 ms; matrix size, 202×182 mm; voxel size, 1.6×1.6×8.0 mm; bandwidth, 962 Hz/Px; flip angle (FA), 47°; slice thickness, 8 mm; and inter slice gap 2, mm.	Location and pattern of LGE lesions, left and right ventricle function parameters	One patient (2.5%) had positive LGE located at the mid-inferior wall Global Native T1 (ms) median 1137.5 (IQR 1099.3-1195.3) Global Pericardial T1 (ms) median 641.5 (IQR 599.8-689.5)
Myhre, 2021	Prospective, single-center observational study	N=58 Age 56 (Q1-Q3 50-70) 56% male	The time from hospital admission	The CMRs were conducted at Akershus University Hospital between	Ventricular volumes and EF and mass, presence of scar.	Myocardial scar non-20.5%, scar volume 2

		Admitted 100%; mechanical ventilation in the ICU 19%	to the CMR examination was median 175 (IQR 105-217) days	June 24 and November 18 2020 on a 1.5 MRI scanner. Short-axis, steady-state-free precession sequences were acquired in contiguous 8 mm short axis slices for assessing ventricular volumes and ejection fraction. T2 STIR images were acquired in 10 mm slices in a single midventricular short axis view and 1 four and 1 left ventricular 2 chamber views. Two-dimensional, phase sensitive inversion recovery LGE imaging in contiguous 10 mm short-axis slices covering the ventricles and 3 long-axis views for assessing myocardial scarring was performed starting 10 minutes after injection of 0.15 mmol/kg gadoterate meglumine (Clariscan Gé, GE Healthcare). Myocardial T1 and T2 mapping sequences for the assessment of diffuse myocardial fibrosis and edema were acquired in single 10 mm	Presence of LGE (myocardial scar) or left ventricular EF (LVEF) < 50% were defined as abnormal CMR.	1.8%; Myocardial scar ICU 9.1% (n= scar volume 1.9%; Native T1 non-ICU 1010 ± 3 ms; Native T1 ICU 989 ± ms; Native T2 non-ICU ± 2.9 ms; Native T2 ICU 52.1 2.3

				midventricular short-axis slices. T1 maps were acquired before and 15 minutes after contrast administration using MOLLI sequences with 5s (3s) 3s and 4s (1s) 3s (1s) 2s mapping schemes, respectively. A gradient-spin echo sequence was used for T2 mapping.		
Pan, 2021	Prospective, single-center, observational cohort study	N=21 Age 36 (IQR 31–47) 47.6% male COVID-19 severity: Mild 19%; moderate 67%; severe 14%; critical 0%	Median 46 days (IQR 43–50) between confirming COVID-19 and CMR examination	MRI was performed on clinical 3-T scanners. The MRI scanning protocol included: 1) conventional sequences: short-axis and long-axis cine and T2-weighted imaging (T2WI), and 2) quantitative mapping sequences: native T1/T2 mapping. The stack of short-axis slices covered the left ventricle (LV) from apex to mitral annulus. The imaging plane of T2WI and native T1/T2 mapping were set as the short-axis cine.	Myocardial edema, myocardial T1/T2 values, left and right ventricle function parameters	Myocardial native, T1 (msec) 1208.4 ± 64.2 Myocardial native, T2 (msec) 49 (IQR 46.1, 54.6) Taking at least 2 times above the mean of healthy controls as a cutoff value for abnormal myocardial T1 (1337 msec) or T2 value (59 msec), 13 (61.90%) patients recovered from COVID-19

						19 had abnormal myocardial performance including raised myocardial native T1 value (5/2 [23.81%], involving 2.30% [7/304] of segments and raised myocardial native T2 value (10, [47.62%], involving 7.69% [25/325] of LV segments
Puntmann, 2021	Prospective observational cohort study	N=100 Age 49 ± 14 53% male COVID-19 severity: Asymptomatic 18%; minor to moderate symptoms 49%; hospitalized 33%	Median (IQR) time between positive testing and CMR was 71 (64-92) days	Cardiac magnetic resonance imaging was performed on clinical 3-T scanners using standardized and unified imaging protocols. Conventional sequences were used for acquisition of cardiac function, volumes, mass, and scar imaging. Myocardial T1 and T2 mapping were acquired in a single midventricular short-axis slice using a	Cardiac involvement and myocardial inflammation.	Raised myocardial native T1 (73%), raised myocardial native T2 (60%), myocardial LGE (32% or pericardial enhancer (22%) 12% had an ischemic-type pattern of myocardial LGE.

				validated variant of a modified Look-Locker Imaging sequence, whereas for T2 mapping, a validated sequence for measurement of myocardial edema was used (T2-FLASH). Due to the proven sensitivity of Goethe CVI MOLLI for abnormal myocardium and evidence of superior diagnostic and prognostic performance, postcontrast T1 mapping was not part of the standardized protocol. LGE imaging was performed approximately 10 minutes after administration of 0.1 mmol/kg of body weight of gadobutrol.	

Ulloah, 2021	Prospective, single-center observational study	N=57 Age 59 ± 15 80.7% male Admitted 100% ICU 7%	The contact-to-CMR interval was 81 ± 27 days.	CMR studies were carried out with a 1.5 Tesla device using a 32-channel multi-element surface antenna and ECG synchronization. The cine images, taken in end-expiration with a retrospective ECG protocol, were captured using conventional steady-state free-precession (SSFP) sequences in longitudinal axes with 2-, 3- and 4-chamber views and in 10–15 contiguous short-axis (SAX) slices covering both ventricles base to apex. Non-contrast CMR exams in control group. In study group, approximately 8–10 min after intravenous infusion of 0.15 mmol/kg of gadobutrol, LGE images were acquired, in the same views as for the cine images, employing a T1-weighted gradient echo inversion-recovery (IR) sequence.	Cardiac functional analysis, presence of focal myocardial oedema, LGE.	LGE 26.3 - non ischemic 19.3% - ischemic 3.5% - pericard 3.5% Native T1 996.4 ± 4 ms T2 mapping 50.9 ± 4.1 ms

Wang, 2021	Prospective, single-center observational study	N=44 Age 47.6 ± 13.3 43.2% male COVID-19 severity: Moderate 73%; Severe 25%; Critical 2%	102.5 ± 20.6 days between hospital discharge and CMR	All patients underwent CMR on a 3 T CMR scanner (Ingenia CX, Philips Healthcare, Best, The Netherlands). The CMR protocol consisted of black blood fat-suppressed T2 weighted imaging (T2w), T2 star mapping, left ventricle (LV) cine imaging including four chambers, two-chamber, short axis, pre- and post-contrast T1 mapping, and LGE.	The visual presence and different patterns on the LGE images, ratio between the LGE volume and the total LV myocardium volume (LGE/myocardium) in the LGE-positive patients.	No myocardial hemorrhage was observed in any patient; however, LGE was detected in 13 patients (29.5%). LGE lesions were located in the middle myocardium and/or subepicardium with a scattered distribution.

LGE: Late gadolinium enhancement

Zoeken en selecteren

Clinical question

What is the value of cardiac MRI in post-acute care for patients with persisting cardiac complaints after COVID-19?

PICO 1

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of COVID-19)

I: Post-acute care including the use of CMR

C: Post-acute care without the use of CMR

O: Patient satisfaction, quality of life, treatment consequences (medication, number of interventions)

Other selection criteria

Study design: systematic review, RCT, observational study

Follow-up: at least 4 weeks after COVID-19 onset

Study population: at least 10 patients per study arm

PICO 2

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of COVID-19)

I: CMR

C: -

O: Cardiac conditions for which treatment/follow-up is indicated (ischemia, myocarditis, myocardial infarction)

Other selection criteria

Study design: systematic review, observational study

Follow-up: at least 4 weeks after COVID-19 onset

Study population: at least 20 patients per study

The working group considered it probable that intervention studies as indicated by PICO 1 have not yet been published. In case no studies were found in line with PICO 1, the systematically searched literature would be used to describe findings by CMR, as indicated by PICO 2. This evidence cannot be graded.

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2019 up to and including May 4, 2021. The search was updated on September 7, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). No studies were found to support PICO 1. Studies were selected based on the criteria as described in PICO 2. Studies published between May 4 and September 9, 2021 were included only if (1) the results were divergent from the prior conclusions; (2) the results provided new insights; or (3) the study population was very large (>1000 patients). The appendices (*Bijlagen*) contain the PRISMA flowcharts of the first search and the update, showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group did not define the outcome measures a priori but followed the definitions used in the studies. For PICO 2, the working group considered LGE, T1 and T2 values relevant for determining ischemia, inflammation or myocarditis even though cut-off points cannot be defined.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Meetinstrumenten na COVID-19

Uitgangsvraag

Welke domeinen van de gezondheidsstatus zijn zinvol om in kaart te brengen binnen de ziekenhuissetting op de polikliniek bij patiënten met aanhoudende klachten na COVID-19? En welke set meetinstrumenten heeft de beste testeigenschappen?

Aanbeveling

Breng bij patiënten die na doorgemaakte COVID-19 gezien worden in de polikliniek met gevalideerde meetinstrumenten in kaart welke beperkingen in functioneren zijn ontstaan. Betrek hierbij ongeacht het klachtenpatroon alle 4 de domeinen:

- somatisch
- psychisch
- functioneel
- sociaal

Overwegingen

Voor- en nadelen van de interventie

De huidige kwaliteitsdocumenten raden aan dat er follow-up plaatsvindt van patiënten die COVID-19 hebben doorgemaakt en aanhoudende klachten ervaren. Het doel van nazorg voor COVID-19-patiënten in de tweede lijn is om somatiek uit te sluiten danwel aan te tonen en in kaart te brengen op welke domeinen - fysiek, functioneel, sociaal of psychisch - er eventueel problemen zijn die aandacht behoeven. Vanuit de polikliniek kan de patiënt verwezen worden naar disciplines in de eerste lijn, zoals oefen-/fysiotherapie, ergotherapie, diëtetiek, logopedie, generalistische basis-ggz of naar een praktijkondersteuner geestelijke gezondheidszorg (POH-ggz). Ook kan de patiënt bij complexere problematiek worden doorverwezen binnen de tweede lijn naar bijvoorbeeld een revalidatiearts, geriater, cardioloog, neuroloog of psychiater. Bij arbeidsgerelateerde problematiek kan hij doorverwezen worden naar de bedrijfsarts of reïntegratiedeskundige voor nadere analyse en begeleiding.

Met behulp van meetinstrumenten kan tijdens de follow-up een beeld verkregen worden van het algeheel functioneren na doorgemaakte COVID-19. Daarbij is het van belang om dit te vergelijken met het premorbide niveau van functioneren om zo een goed beeld te krijgen van de ontstane beperkingen na doorgemaakte COVID-19. De behandeling kan hierop toegespitst worden en zo aansluiten bij de hulpvraag van de patiënt. Ook kan door het herhaaldelijk afnemen van de test de voortgang worden beoordeeld.

Patiënten worden meestal niet langdurig gevolgd in de tweede lijn. Enige uniformiteit in het gebruik van meetinstrumenten in de eerste lijn, ziekenhuis en geriatrische revalidatiezorg (GRZ) of medisch-specialistische revalidatiezorg is dan ook van belang, zodat de patiënt goed kan worden overgedragen en de voortgang kan worden bepaald. Door de verschillende settings kunnen er echter wel verschillen zijn in de keuze voor meetinstrumenten. In het ziekenhuis wordt de patiënt (soms meerdere keren) gezien, en is de tijd in de

sprekkamer relatief beperkt. Dit in tegenstelling tot de GRZ of MSR, waar de patiënt verblijft of een langdurig poliklinisch behandeltraject heeft. Voor handvatten voor geschikte meetinstrumenten binnen de MSR/GRZ verwijzen we naar de module 'Meetinstrumenten binnen de MSR/GRZ' (VRA en Verenso, 2021).

Uit de literatuuranalyse blijkt dat er nog geen systematische reviews beschikbaar zijn waarin de psychometrische eigenschappen zijn onderzocht van een set van meetinstrumenten waarmee de gezondheidsstatus van patiënten na doorgemaakte COVID-19 in kaart kan worden gebracht. Daarnaast zijn er geen internationale richtlijnen of publicaties gevonden waarin specifieke sets van meetinstrumenten voor deze groep patiënten zijn vergeleken. Vanwege de afwezigheid van literatuur kiest de werkgroep ervoor om, op basis van expert opinie, aanbevelingen te formuleren over welke domeinen gemeten zouden moeten worden. Gezien het grillige en onvoorspelbare beloop en de soms lange periode van herstel bij COVID-19 pleit de werkgroep bij de follow-up voor een holistische benadering van de patiënt. Hierbij is niet alleen het somatisch functioneren belangrijk, maar zijn ook de psychische, functionele en sociale aspecten zeer relevant. De werkgroep heeft er gezien de afwezigheid van literatuur voor gekozen om niet een set meetinstrumenten strikt voor te schrijven. Er worden wel voorbeelden gegeven van meetinstrumenten die gebruikt kunnen worden in de praktijk.

Tabel 1 geeft de domeinen weer die bij voorkeur in kaart worden gebracht, en geeft voorbeelden van vragenlijsten waarmee deze domeinen geïnterviewd kunnen worden. Voor het bepalen van de domeinen zijn we uitgegaan van de verschillende domeinen die in generalistische beroepsgroepen gebruikt worden (NVKG, 2010; Verenso, 2020; VRA, 2020) en het patroon en de diversiteit van de klachten en functiestoornissen die internationaal uitgebreid beschreven zijn tijdens het beloop van het herstel na COVID-19. Per instrument staat beschreven of deze thuis kan worden ingevuld of dat deze in de spreekkamer moet worden afgenomen en hoeveel tijd het kost om het meetinstrument in te vullen/af te nemen. Hoewel geen van deze vragenlijsten specifiek gevalideerd zijn voor patiënten die COVID-19 hebben doorgemaakt, zijn er op het eerste gezicht geen concrete redenen dat ze niet geschikt zouden zijn bij deze patiëntengroep. Hoewel er variatie is tussen meetinstrumenten de tijdsbelasting van de individuele meetinstrumenten redelijk beperkt is en de belasting voor patiënten beperkt is, zijn de resultaten/eindscores eenduidig te interpreteren en zijn er veelal normwaarden beschikbaar.

Uit **tabel 1** blijkt dat er voor de meeste domeinen meerdere opties beschikbaar zijn. Bij de samenstelling van de set meetinstrumenten dient onder andere rekening te worden gehouden met:

- Het individueel in kaart brengen van patiënten. Gezien de grote variatie tussen patiënten moeten er per individu relevante domeinen geïdentificeerd worden.
- De individuele belastbaarheid van de patiënt. Zeker bij de fysieke testen is het belangrijk om de patiënt niet te overbelasten.
- Bij de ontwikkeling van een set meetinstrumenten kan het samenvoegen van domeinen leiden tot redundantie, waardoor een vragenlijst onnodig lang wordt en weinig verschillende aspecten meet (vanwege overlap).

Mochten er andere meetinstrumenten zijn die niet in **tabel 1** gerapporteerd staan maar wel geschikt lijken, dan is het belangrijk dat de klinimetrie (validiteit, betrouwbaarheid en responsiviteit) in acht genomen wordt

voordat de meetinstrumenten in de praktijk gebruikt worden.

Tabel 1. Meetinstrumenten in de tweede lijn

<u>Domein</u>	Vragenlijst	Thuis	Spreekkamer	
Functioneel				
ADL	EQ5D	2-5 minuten		
	KATZ-ADL			
	Barthel index			
	USER			
IADL /participatie	USER-P restrictie	5 minuten		
	70+ Fillenbaum	5 minuten		
	Amsterdamse IADL vragenlijst			
Voeding	SNAQ65+	5 minuten		
	MNA			
Somatisch				
Fysiek functioneren/ inspanning	Handknijpkracht		5 minuten	
	PROMIS schaal lichamelijk functioneren	2 minuten		
	FACC			
	30 sec sit to stand			
	DEMMI			
	10MWT, 6MTW, 2MWT			
	TUG			
	SPPB			
Vermoeidheid	FSS	5 minuten		
	CIS	5-10 minuten		
	SF-36	9 minuten		
	VAS	1 minuut		
Psychisch				
Stemming	HADS	2-5 minuten		
	EQ-5D-5L			
	BDI			

	GDS			
Cognitie	MOCA		20 minuten	
	6-CIT		2-3 minuten	
	MMSE		15 minuten	
	CFQ	5-10 minuten		
Sociaal				
Inclusief arbeidsparticipatie	USER-P	5 minuten		

Er is gekozen voor een overzichtelijke tabel met een beperkt aantal meetinstrumenten per domein, die qua uitvoerbaarheid en tijdsinvestering goed toepasbaar zijn in de tweede lijn. Keuze voor het meetinstrument is afhankelijk van de voorkeur van de behandelaar, gebaseerd op ervaring en beschikbaarheid.

Bij meer complexe problematiek en/of wens tot verrichten van uitgebreidere klinimetrie verwijzen we naar de tabel met meetinstrumenten in de module 'Meetinstrumenten binnen de MSR/GRZ' (VRA en Verenso, 2021).

Kwaliteit van bewijs

Er zijn geen onderzoeken gevonden; de kwaliteit van het bewijs is daarmee zeer laag.

Waarden en voorkeuren van patiënten

Voor patiënten is het belangrijk om zo spoedig en volledig mogelijk te herstellen van COVID-19. Ze hebben vaak behoefte aan diagnostiek naar eventuele onderliggende (behandelbare) oorzaken van hun klachten danwel geruststelling. Het is belangrijk om de hulpvraag van de patiënt goed, zoveel mogelijk in 1 keer en met een relatief lage belasting (qua tijd en moeite) te inventariseren. De inzet van een set meetinstrumenten kan daarbij ondersteunen.

De meeste patiënten ervaren het als een meerwaarde om de uitslag van de meetinstrumenten te bespreken. Het kan de patiënt inzicht geven en kan motiverend werken. Daarnaast is het voor de patiënt van meerwaarde om waar nodig geïndividualiseerde interventies te kunnen ontvangen.

Kosten

Er worden geen noemenswaardige voordelen of bezwaren gezien ten aanzien van de kosten. Aanschaf van gevalideerde vragenlijsten kan theoretisch gezien kosten met zich meebrengen. Een groot deel van de meetinstrumenten is echter kosteloos te vinden op bijvoorbeeld <https://meetinstrumentenzorg.nl>. Een deel zal ook binnen het ziekenhuis al aanwezig zijn. Het is wenselijk, maar niet noodzakelijk, om de vragenlijsten digitaal in te laten vullen, zodat ze meteen zichtbaar worden in het elektronisch patiëntendossier (EPD). In ziekenhuizen waar dit nog niet mogelijk is, zal de eventuele implementatie van de vragenlijsten in het EPD kosten met zich meebrengen. De tijdsinvestering die het een hulpverlener kost om de test(s) af te nemen, is te overzien en wordt verminderd door de patiënt een groot deel van de meetinstrumenten al voorafgaand aan het polibezzoek in te laten vullen.

Aanvaardbaarheid

Binnen het ziekenhuis wordt al gewerkt met meetinstrumenten. Vanuit het werkveld was er echter behoefte om het klinisch beeld en het beloop van COVID-19 uniformer in kaart te brengen (zie bijlage: Verslag invitational conference). Aangezien er al ervaring is met het gebruik van gevalideerde meetinstrumenten binnen de ziekenhuissetting verwacht de werkgroep geen problemen met betrekking tot de aanvaardbaarheid.

Haalbaarheid

De afname van meetinstrumenten en vragenlijsten is tegenwoordig steeds meer verweven met de mogelijkheden in het EPD. Dit kan tijdsbesparing en een efficiëntere werkwijze opleveren. Daarentegen blijft de balans cruciaal tussen de beschikbare behandeltime per patiënt en de tijdsinvestering van de afname van meetinstrumenten en vragenlijsten. Om de beperkte tijd in de spreekkamer doelmatig en efficiënt te gebruiken, kunnen patiënten voorafgaand aan de COVID-19 poli een vragenlijst opsturen die ze thuis invullen en meenemen naar het polibezoek. Daarnaast zijn er meetinstrumenten die alleen door een professional afgenomen worden. Hiervoor kan bijvoorbeeld ook een (gespecialiseerd) verpleegkundige of paramedicus ingezet worden. Gezien de lage kosten en de beschikbaarheid van de instrumenten verwachten we geen problemen met betrekking tot de haalbaarheid.

Waarom deze aanbeveling/rationale?

Hoewel er nog weinig bewijs is over de klinimetrische eigenschappen van meetinstrumenten bij patiënten die COVID-19 hebben doorgemaakt, en er in internationale richtlijnen nog geen set van meetinstrumenten zijn beschreven, is de werkgroep wel van mening dat het in kaart brengen van specifieke domeinen een onmisbaar deel uitmaakt van de nazorg in het ziekenhuis. Naast de aanbeveling welke domeinen in kaart te brengen, geeft de werkgroep per domein enkele meetinstrumenten die gebruikt kunnen worden in de praktijk om voor meer uniformiteit te zorgen.

Onderbouwing

Achtergrond

Het klinisch beeld en beloop van COVID-19 verschillen per stadium (acuut/subacuut/chronisch) en zijn onder andere afhankelijk van het premorbide niveau van functioneren. Op dit moment worden er verschillende meetinstrumenten gebruikt in verschillende stadia van herstel om de domeinen van functioneren en de gezondheidsstatus in kaart te brengen. Er is op dit moment nog veel praktijkvariatie in wat er gemeten wordt, welke test hiervoor gebruikt wordt en wanneer deze testen afgenomen worden.

Zoeken en selecteren

Clinical question

Which health domains are useful to assess in ambulatory patients with persisting complaints after COVID-19? And which set of instruments has the best characteristics?

PICO

P: Patients with persisting complaints after COVID-19 (≥ 4 weeks from onset of COVID-19)

I: set of instruments to determine health status for different domains: social (including participation), somatic, functional, and psychological.

C: other set of instruments to determine health status individual instruments to determine health status

O: Validity (critical), Reliability (critical), Responsiveness (critical)

Other selection criteria

Study design: guideline or systematic review

Follow-up: not specified

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from January 2019 until June 16, 2021. The search was updated on September 7, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). No studies were found to support PICO 1. Therefore, studies were selected based on the criteria described in PICO 2. Studies published between June 16 and September 9, 2021 were included only if (1) the results were divergent from the prior conclusions; (2) the results provided new insights; or (3) the study population was very large (>1000 patients). The appendices (*Bijlagen*) contain the PRISMA flowcharts of the first search and the update, showing the number of hits, and the reasons for exclusion.

Relevant outcome measures

The working group defined measurement properties a priori according to the taxonomy of the Consensus-based Standards for the selection of health Measurement Instruments (COSMIN) (Mokkink, 2010).

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

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MRI-hersenen na COVID-19

Uitgangsvraag

Wat is de waarde van MRI-hersenen in de nazorg voor patiënten met aanhoudende neurologische klachten na COVID-19?

Aanbeveling

Verricht geen MRI-hersenen bij COVID-19-patiënten met aanhoudende neurologische klachten, tenzij er een andere neurologische ziekte in de differentiaaldiagnose staat waarvoor dit geïndiceerd is.

Overwegingen

Voor- en nadelen van de interventie

Het uitvoeren van MRI-hersenen bij patiënten met aanhoudende neurologische klachten na doorgemaakte COVID-19 wordt op dit moment niet standaard gedaan. Een mogelijk voordeel is dat de MRI-hersenen een relevante afwijking toont, waardoor het behandelplan verandert. MRI-hersenen bij patiënten met aanhoudende neurologische klachten na doorgemaakte COVID-19 laat echter zelden relevante afwijkingen zien. Er is geen prospectief vergelijkend onderzoek gedaan tussen patiënten met en zonder neurologische klachten na doorgemaakte COVID-19 en de afwijkingen op MRI-hersenen hierbij. Er is ook geen relatie aangetoond tussen de afwijkingen op MRI-hersenen en neurologische klachten.

De literatuurzoekactie leverde 2 relevante studies op. Hosp (2021) beschreef een prospectief onderzoek waarbij 13 patiënten gemiddeld 30,5 dagen na presentatie met COVID-19 een MRI-hersenen ondergingen vanwege het ontstaan van minimaal 2 nieuwe neurologische klachten, gedefinieerd als veranderde reuk, veranderde smaak, cognitieve stoornissen of uitvalsverschijnselen bij neurologisch onderzoek, waarbij er op dat moment geen sprake meer was van SARS-COV-2-infectie. Bij 4 patiënten waren er micro-embolische subacute infarcten zichtbaar; bij 1 van deze patiënten waren er ook klinische tekenen van cerebrale ischemie. De cognitieve klachten bij deze patiënten konden niet middels de afwijkingen op MRI-hersenen worden verklaard. Er werden geen andere structurele afwijkingen gezien.

Marcic (2021) beschreef een observationele studie waarin bij 39 patiënten met COVID-19 (en 16 voor leeftijd geselecteerde gezonde controlepersonen) een MRI-hersenen werd verricht 40-60 dagen na herstel van de SARS-COV-2-infectie, vanwege non-specifieke neurologische symptomen, zoals veranderde reuk en/of smaak, hoofdpijn, duizeligheid en vermoeidheid. Bij alle patiënten werden op MRI-hersenen meerdere puntvormige witte stofafwijkingen gezien, die zich met name bilateraal periventriculair, frontaal subcorticaal of frontoparietaal juxtacorticaal bevonden, zonder aanwijzingen voor vasculitis of recente ischemie, geduid als microvasculaire schade bij COVID-19. Bij de controlegroep van 16 gezonde patiënten zonder doorgemaakte COVID-19 werden deze afwijkingen niet gevonden. Er was geen relatie tussen het aantal afwijkingen en de mate van smaak- en reukverlies of duizeligheid.

Beide onderzoeken hebben methodologische tekortkomingen en daardoor een hoog risico op bias. Bij het eerste onderzoek is er geen nadere uitleg gegeven over welke neurologische klachten er op dat moment bestonden en of de MRI-hersenen per klacht nog specifieke afwijkingen oplevert. Bij het tweede onderzoek is

er niet gekeken naar cognitieve klachten die het grootste aandeel vormen van de klachten waarvoor patiënten na doorgemaakte COVID-19 bij de neurologie terecht komen. Bij beide onderzoeken is er geen follow-up gedaan, waarbij onzeker is of deze afwijkingen en klachten in de loop der tijd nog zouden kunnen verbeteren of herstellen.

Een ander onderzoek waarbij de MRI-hersenen bij patiënten met doorgemaakte COVID-19 vergeleken werd met patiënten zonder doorgemaakte COVID-19 toonde geen significant verschil in het voorkomen van microvasculaire schade tussen beide patiëntengroepen (Lu, 2020). In de patiëntengroep met doorgemaakte COVID-19 was er bij 55% sprake van aanhoudende neurologische klachten zoals hoofdpijn, wisselende stemming, geheugenklachten en reuk- en smaakverlies op het moment dat de MRI-hersenen verricht werd; dit was 3 maanden na de start van de klachten, zonder dat er verschil was in de MRI-hersenen tussen de patiëntengroepen met en zonder neurologische klachten na COVID-19-infectie. Wel werd bij de patiënten met doorgemaakte COVID-19, onafhankelijk van het bestaan van neurologische klachten, een significant groter grijzestofvolume van de hippocampus en olfactoire cortex gezien, wat mogelijk kan duiden op neurogenese. In een biobankonderzoek uit 2021 werd echter gezien dat de MRI-hersenen van patiënten na doorgemaakte COVID-19 vergeleken met de MRI-hersenen voor SARS-COV-2-infectie afname van grijze stof liet zien in de parahippocampale gyrus en de orbitofrontale cortex (preprint Douaud, 2021). Beide bevindingen hebben geen klinische consequenties.

Er is geen wetenschappelijk bewijs voor de meerwaarde van een MRI-hersenen bij aanhoudende klachten na COVID-19. De beschreven onderzoeken tonen namelijk aan dat er weliswaar afwijkingen gezien kunnen worden, maar dat deze geen behandelconsequenties hebben. Het is bovendien onzeker of er een relatie is met de kliniek. Bij patiënten waar een andere diagnose in de differentiaaldiagnose staat, kan beeldvorming uiteraard wel geïndiceerd zijn. Met name als er objectieveerbare afwijkingen bij het neurologisch of neuropsychologisch onderzoek gevonden worden, kan er een goede reden zijn om wel beeldvorming te verrichten.

Kwaliteit van het bewijs

Er is literatuuronderzoek gedaan naar de waarde van het inzetten van MRI-hersenen bij aanhoudende neurologische klachten na doorgemaakte COVID-19. Er zijn geen onderzoeken gevonden die dit hebben beschreven. Ook is er geen vergelijkend onderzoek gevonden tussen patiënten met en zonder neurologische klachten na COVID-19 en de bevindingen op MRI-hersenen.

Daarom wordt de tot op heden gepubliceerde literatuur over bevindingen op MRI-hersenen bij patiënten met neurologische klachten na doorgemaakte COVID-19 exploratief beschreven. De kwaliteit van het bewijs is zeer laag. In de besluitvorming gaan we daarom uit van de aanvullende argumenten, waaronder expert opinie van de werkgroepleden, waar mogelijk aangevuld met (indirect) bewijs.

Waarden en voorkeuren van patiënten

Aanhoudende neurologische klachten na doorgemaakte COVID-19 komen regelmatig voor en leiden tot een verminderde kwaliteit van leven (Graham, 2021). Patiënten met deze klachten worden hierdoor regelmatig verwezen naar de neurologie om deze klachten te analyseren en te behandelen, waarbij er ook behoefte kan zijn aan aanvullend onderzoek om de klachten te objectiveren. Bij gebrek aan bewijs voor zinvolheid is er geen indicatie om standaard een MRI-hersenen te verrichten. Verder is er een grote kans op

toevalsbevindingen, wat juist kan leiden tot een toename van onrust en niet-zinnige aanvullende diagnostiek in het kader van de klachten (O'Sullivan, 2018). Ook is bekend dat het geruststellingseffect na MRI-hersenen slechts gedurende 1 jaar aanhoudt (Howard, 2005).

Kosten

De kosten van een MRI-hersenen zijn gemiddeld € 190. Er kunnen aanvullende kosten ontstaan als er toevalsbevindingen worden gevonden, waarna verder aanvullend onderzoek nodig is, zoals aanvullende opnames of herhaling van de MRI-hersenen na een bepaalde periode. Op basis van literatuuronderzoek en de conclusie van de werkgroep wordt de huidige praktijk niet veranderd en zijn er geen verschillen in kosten.

Aanvaardbaarheid

Op basis van literatuuronderzoek en de conclusie van de werkgroep wordt de huidige praktijk niet veranderd en zijn er geen verwachte problemen met de aanvaardbaarheid.

Haalbaarheid

Op basis van literatuuronderzoek en de conclusie van de werkgroep wordt de huidige praktijk niet veranderd en zijn er geen verwachte problemen met de haalbaarheid en implementatie.

Waarom deze aanbeveling?

MRI-hersenen bij patiënten met aanhoudende neurologische klachten na doorgemaakte COVID-19 laat zelden relevante afwijkingen zien. Er is geen goed vergelijkend onderzoek bekend tussen patiënten met en zonder neurologische klachten na doorgemaakte COVID-19 en de afwijkingen op MRI-hersenen hierbij, maar het beschikbare bewijs toont geen relevante verschillen met klinische consequenties. De wetenschappelijke literatuur biedt onvoldoende houvast over de relatie tussen de afwijkingen en neurologische klachten. Bij patiënten met aanhoudende neurologische uitval na COVID-19 kan er sprake zijn van een andere diagnose die de klachten verklaart, maar dit werd in het literatuuronderzoek niet onderzocht en hier is dan ook geen verdere uitspraak over te doen. Bij patiënten bij wie een andere diagnose in de differentiaaldiagnose staat, kan beeldvorming uiteraard wel geïndiceerd zijn. Met name als er objectiveerbare afwijkingen bij het neurologisch of neuropsychologisch onderzoek gevonden worden, kan er een goede reden zijn om wel beeldvorming te verrichten.

Onderbouwing

Achtergrond

Een deel van de patiënten met een doorgemaakte COVID-19 heeft langdurige klachten en/of een incompleet herstel (zie de module [Natuurlijk beloop](#)). Deze patiënten beschrijven vaak ook neurologische klachten. Dit betreft meestal cognitieve klachten zoals concentratiestoornissen en overprikkeling, maar zij beschrijven ook hoofdpijn en slaapstoornissen (The Lancet Neurology, 2021). In de analyse van neurologische klachten na doorgemaakte COVID-19 is het de vraag of aanvullend onderzoek bijdraagt aan het stellen van de diagnose postinfectieuze neurologische klachten na COVID-19 en voor patiënttevredenheid zorgt. Het is onduidelijk of beeldvorming middels MRI in het kader van deze klachten een bijdrage kan leveren aan revalidatie, behandelconsequenties heeft en of het uitvoeren van MRI-hersenen geïndiceerd is.

Conclusies / Summary of Findings

It is unclear whether the use of brain MRI affects patient satisfaction, quality of life or treatment consequences after COVID-19.

Samenvatting literatuur

No studies were included in the analysis of the literature. No studies were found to support PICO 1. Regarding PICO 2, the first search resulted two observational studies published before June 16, 2021. A descriptive summary of brain MRI findings (PICO 2) is presented in table 1. The updated search did not result in additional studies. Due to the explorative nature of the data, the evidence could not be graded.

Table 1. Study design and results

Reference	Study design	Population	Cerebral MRI	Timing of imaging	Study outcomes	Results
Hosp, 2021	Prospective study	N=29 Age 62.2 ± 14.4 62% male	13 patients with signs of a possible COVID-19-related encephalopathy (defined by two or more new neurological symptoms) underwent cerebral Mri. On a 3 T scanner (Magnetom Prisma, Siemens Medical Solutions) with a 64-channel head coil including the following sequences: sagittal 3D T1-weighted magnetization prepared rapid gradient echo (MP-RAGE) before and after contrast agent administration, sagittal 3D FLAIR SPACE (sampling perfection with application-optimized contrasts using different flip	30.5 ± 13.4 days after symptom onset.	Olfaction and gustation. Cognitive functions.	Critical outcomes: In four patients (30%), microembolic subacute infarcts were observed (n = 1 bilateral cerebellar; in n = 1 each, pinhead-sized lesions were located in the right corona radiata, the left superior cerebellar peduncle and the right frontal cortex). Other outcomes: No other structural changes, and in particular no sign of atrophy, acute encephalitis or leptomeningeal enhancement, were found.

			angle evolutions), axial susceptibility-weighted imaging (SWI), axial proton density + T2 double echo, dynamic susceptibility contrast (DSC) perfusion imaging and diffusion mesoscopic imaging with 61 diffusion-encoding directions and b-factors of 1000 and 2000 s/mm², evaluated by a board-certified neuroradiologist (H.U.). (15 patients underwent FDG PET. All PET scans were acquired on a fully digital Vereos PET/CT scanner (Philips Healthcare). PET emission data were acquired 50 min after the injection of 215 (13) MBq 18FDG for 10 min.)			
Marcic, 2021	Cross-sectional observational study	N= 55 Age 37.9 (35 to 40) 60% male	Brain MRI scans of the included patients with persistent neurological symptoms was performed at 3	40 to 60 days after recovery from SARS-CoV-2 infection.	Ultrasound examination of the blood vessels of the neck (ACI, ACE, VA) on the same day	Critical outcomes: The DWI sequence showed no signs of infarction in any of the patients. Other outcomes:

Tesla Skyra MRI scanner (Siemens Healthcare). We did all standard and additional sequences: T1-weighted imaging (axial, sagittal), fluid-attenuated inversion recovery —FLAIR (axial), T2-weighted imaging (axial, coronar), T2* susceptibility-weighted imaging (or T2*-weighted gradient-recalled echo if susceptibility-weighted imaging is not available), diffusion-weighted imaging with both a trace image and an apparent diffusion coefficient map (axial), CISS and with T1-weighted imaging enhancement. All included patients receiving paramagnetic contrast agent intravenously (gadoterate meglumine, dose 0.2 mL/kg). The T1 sequence was made from the postcontrast sequences. The

of the brain MRI. VAS scale to assess the strength of the headache.

Patients with moderate SARS-CoV-2 infection had a statistically significantly higher number of brain lesions ($z = 5.3$; $p < 0.001$). The median number of lesions by 12.5 (95% CI: 9.7–15.3) is higher in the moderate form of the disease. Coefficient $\rho = 0.469$ ($p = 0.003$). The number of brain lesions significantly correlated with BMI, platelet count, the VAS degree of headache. No association between the number of lesions and damage of smell, taste and vertigo were proved. There was a higher number of lesions in the moderate form of the disease.

		diffusion-weighted trace image and apparent diffusion coefficient map are important for excluding recent infarcts. Sequence parameters should be consistent with recommendations for neuroimaging from the American College of Radiologists. Additionally, we did MR angiography. All brain MRI findings were interpreted by two board-certified		

Values are shown as mean $\pm$ SD unless indicated otherwise.
neuroradiologists.

Zoeken en selecteren

Clinical question

What is the value of MRI of the brain in post-acute care for patients with persisting neurological complaints after COVID-19?

PICO 1

P: Patients who have experienced COVID-19 (≥ 4 weeks from onset of acute COVID-19)

I: Rehabilitation by the use of MRI of the brain

C: Rehabilitation without the use of MRI of the brain

O: Patient satisfaction, quality of life, findings on MRI that have treatment consequences (medication, number of interventions)

Other selection criteria

Study design: SR, RCT

Follow-up: at least 4 weeks after COVID-19 onset

Study population: at least 10 patients per study arm

PICO 2

P: Patients in the subacute/late phase after COVID-19 infection (≥ 4 weeks)

I: MRI of the brain

C: -

O: Structural brain damage for which treatment/follow-up is indicated (microbleeds, infarctions)

Other selection criteria

Study design: SR, observational studies

Follow-up: at least 4 weeks after COVID-19 onset

Study population: at least 20

The working group considered it probable that intervention studies as indicated by PICO 1 have not yet been published. In case no studies were found in line with PICO 1, the systematically searched literature would be used to describe findings by brain MRI, as indicated by PICO 2. This evidence cannot be graded.

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2019 up to and including June 17, 2021. The search was updated on September 7, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). No studies were found to support PICO 1. Therefore, studies were selected based on the criteria described in PICO 2. Studies published between May 4 and September 9, 2021 were included only if (1) the results were divergent from the prior conclusions; (2) the results provided new insights; or (3) the study population was very large (>1000 patients). The appendices (*Bijlagen*) contain the PRISMA flowcharts of the first search and the update, showing the number of hits, and the reasons for exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows:

Structural COVID19 related brain damage for which specific treatment could be initiated, such as microbleeds or infarctions, and the influence of these findings on the rehabilitation

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Multidisciplinair overleg na COVID-19

Uitgangsvraag

Wat is de plaats van het multidisciplinair overleg? Wie zouden hier bij voorkeur bij aanwezig moeten zijn?

Aanbeveling

Zorg voor 1 aanspreekpunt of verwijzloket binnen het ziekenhuis waar de huisarts terecht kan voor verwijzing naar of vragen over het multidisciplinaire overleg.

Bespreek doorverwezen patiënten na doorgemaakte COVID-19 (volgens de criteria in de module Multidisciplinaire zorg) indien mogelijk in een multidisciplinair overleg, waarin afhankelijk van de lokale afspraken bij voorkeur vertegenwoordigd zijn:

- een geriater, internist en/of longarts
- een psycholoog
- een revalidatiearts of specialist ouderengeneeskunde
- de huisarts

Overweeg op basis van de patiëntspecifieke problematiek een specifieke andere specialist, paramedicus, sportarts, bedrijfsarts en/of verzekeringsarts te betrekken.

Overwegingen

De klachten zijn uniek noch specifiek voor COVID-19, en helaas is er geen objectieve biomarker om een diagnose te kunnen stellen en behandeling in te zetten. Dit maakt dat patiënten die behoefte hebben aan duiding van hun klachten zich niet gehoord en onderbehandeld kunnen voelen. De psychosociale context en impact op arbeidsparticipatie spelen hierbij eveneens een rol. Bij een deel van de patiënten vergroot dit het risico op shoppen (Burke, 2019). Zowel in Engeland als in Amerika worden deze patiënten – eveneens gebaseerd op expert opinie in een multidisciplinaire opzet behandeld. In Engeland zijn hiervoor zelfs speciale klinieken opgezet.

Voor deze patiënten is een multidisciplinaire, integrale benadering essentieel, zodat patiënten in 1 keer uitgebreid en vanuit verschillende domeinen beoordeeld worden, waarna zo nodig vervolgbeleid kan worden ingezet. Hiermee is de patiënt snel geholpen en voelt hij zich gehoord en gesteund. Bij aanhoudende, eenduidige klachten die niet verbeteren door interventies in de eerste lijn kan de huisarts, afhankelijk van de aard van de klachten, kiezen voor een overleg met een generieke specialist of orgaanspecialist.

Bij aanhoudende klachten spelen vaak meerdere aspecten een rol. Ook zorgt kwetsbaarheid (ouderen/multimorbiditeit) dikwijls voor complexiteit. Uitgebreide diagnostische screening van de patiënt op onder andere de domeinen somatisch, psychisch, functioneel en sociaal, gevolgd door het bespreken van de resultaten in een multidisciplinaire setting, heeft dan de voorkeur. Reeds verricht aanvullend onderzoek, resultaten van eerdere leefstijl- en beweegadviezen en een set meetinstrumenten (zie de module Meetinstrumenten) worden dan meegenomen in de uitgebreide tweedelijns (of 1,5-lijns) diagnostische

assessment. Een multidisciplinaire groep bespreekt vervolgens de resultaten. Mogelijk is dit kosteneffectief, omdat bezoeken aan meerdere specialisten kunnen worden voorkomen. Deze groep kan bestaan uit een beschouwend specialist (geriater, internist, longarts), een psycholoog en een revalidatiearts/sportarts of specialist ouderengeneeskunde, alsmede ook de huisarts en eventuele (eerstelijns) paramedici, afhankelijk van regionale afspraken. Voor arbeidskundige aspecten en re-integratie in werk kunnen de bedrijfsarts of verzekeringsarts worden betrokken.

De werkgroep adviseert verder op basis van de patiëntspecifieke problematiek relevante andere specialisten te betrekken in het multidisciplinair overleg. Afhankelijk van de patiënt en lokale organisatie kan ook de verpleegkundige of verpleegkundig specialist een rol spelen. Er dient een vast aanspreekpunt te zijn voor de patiënt en de huisarts voor coördinatie en overleg.

Indien het behandeltraject vervolgens plaatsvindt in de eerste lijn, blijft de huisarts hoofdbehandelaar. Indien het verdere behandeltraject plaatsvindt in de tweede lijn, blijft de huisarts goed geïnformeerd. Zorg dat het voor de patiënt op ieder moment duidelijk is wie het aanspreekpunt is.

Rationale (waarom deze aanbeveling?)

Veel patiënten met doorgemaakte COVID-19 houden klachten. Het is vooralsnog onduidelijk hoelang men de klachten kan houden. Het enige wat we wel weten is dat een categorie patiënten lang klachten kan houden. Om passende zorg te organiseren, is het advies om indien mogelijk een multidisciplinaire bespreking op te zetten voor deze categorie patiënten, afhankelijk van regionale afspraken. Het doel is om zo snel mogelijk klachten te duiden en eventuele comorbiditeit te inventariseren. Vervolgens kan tot een behandelplan worden gekomen waarbij de psychosociale context en copingstrategie van de patiënt kan worden meegenomen en zo nodig bijgestuurd. Hiermee is de patiënt snel geholpen en voelt hij/zij zich gehoord en gesteund. Daarnaast is het mogelijk kosteneffectief, omdat bezoeken aan meerdere specialisten mogelijk worden voorkomen. Zie voor verwijscriteria uit de eerste lijn de module Multidisciplinaire zorg.

Onderbouwing

Achtergrond

Een deel van de patiënten met doorgemaakte COVID-19 blijft klachten houden, ondanks begeleiding in de eerste lijn (zie de module Natuurlijk beloop). Voor deze patiënten, met een heterogeen initieel beloop van de infectie, komt mogelijk doorverwijzing naar de tweede lijn aan de orde (zie de module Multidisciplinaire zorg). Het is onduidelijk hoe de zorg voor deze patiënten in de tweede lijn optimaal en uniform georganiseerd dient te worden. We willen voorkomen dat we pathologie missen bij een nieuwe ziekte en hiermee minder optimale zorg leveren. Ook willen we voorkomen dat patiënten onnodig verschillende specialisten bezoeken en dat regie ontbreekt. Symptomen zijn veelal aspecifiek en kunnen ook passen binnen aanwezige comorbiditeit of de differentiaaldiagnoses. Dit maakt dat de diagnostiek in de tweede lijn voor deze categorie patiënten multidisciplinair, in samenwerking met de huisartsen, aangepakt dient te worden.

Samenvatting literatuur

Er is voor deze vraag geen literatuuronderzoek uitgevoerd. Door de aard van de vraag is een systematische literatuuranalyse niet zinvol. De aanbevelingen zijn gebaseerd op argumenten waaronder expert opinie van de werkgroep, waar mogelijk aangevuld met niet-systematisch gezochte literatuur.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Startpagina - Behandeling van langdurige klachten na COVID-19

Waar gaan deze richtlijnmodules over?

In deze modules (in herziening) worden er aanbevelingen gedaan over:

- de waarde en invulling van een fysiek trainingsprogramma
- de waarde en invulling van ademhalingsoefeningen, ademspiertraining en/of interventies gericht op stemklachten
- de waarde van inzetten en begeleiding met betrekking tot energiemangement
- de waarde van een psychologische behandeling
- de behandeling van cognitieve klachten
- de waarde van (specifieke) voedingsinterventies
- de waarde van medicamenteuze behandelopties
- de behandeling van reuk- en smaakstoornissen
- de bevordering van terugkeer naar werk
- multidisciplinaire zorg

Voor wie zijn deze richtlijnmodules bedoeld?

Deze richtlijnmodules zijn bedoeld voor alle zorgprofessionals die betrokken zijn bij zorg aan patiënten met langdurige klachten na COVID-19. In de verantwoording van elke module staat beschreven welke verenigingen en organisaties de desbetreffende module hebben geautoriseerd of geacordeerd.

Voor patiënten

Voor patiënten is op [Thuisarts.nl](https://thuisarts.nl) informatie te vinden over COVID-19. Daarnaast is aanvullende informatie beschikbaar op het [Coronaplein](https://coronaplein.nl) en [C-support.nu](https://c-support.nu).

Hoe zijn deze richtlijnmodules tot stand gekomen?

Deze modules zijn ontwikkeld binnen het project 'Richtlijn Langdurige klachten na COVID-19'. In de verantwoording worden het ontwikkelproces en de samenstelling van de stuur-, werk- en klankbordgroep in detail beschreven.

Toepassing

Bij deze richtlijnmodules zijn een e-learning module en een webinar ontwikkeld. De e-learning is bedoeld voor medisch specialisten (met name longartsen, klinisch geriaters, internisten en revalidatieartsen) en huisartsen en is op elk gewenst moment te starten. Deze is geaccrediteerd met 2 punten (ABAN). Op 2 juni 2022 vond een webinar plaats, waarin drie thema's uit de richtlijn worden uitgelicht met specifieke ervaringen en uitdagingen uit de praktijk. [Kijk deze hier terug](#), gebruik het wachtwoord 0a5W%pyi.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Arbeid na COVID-19

Uitgangsvraag

- Welke effecten hebben ≥ 4 weken aanhoudende klachten na COVID-19 op het functioneren op werk (en/of opleiding)?
- Wat zijn de bevorderende en belemmerende factoren voor werkhervatting?
- Welke adviezen zijn er voor zorgprofessionals om de terugkeer naar werk bij patiënten met ≥ 4 weken aanhoudende klachten na COVID-19 te bevorderen?

Aanbeveling

Leg uit dat de kans groot is dat klachten spontaan herstellen. Verreweg de meeste patiënten kunnen < 6 maanden na COVID-19 hun werk hervatten, al dan niet met enige aanpassing.

Vraag de werk(zoek)ende patiënt contact op te nemen met de bedrijfs- of verzekeringsarts indien:

- de eigen werkzaamheden zodanig belastend zijn of niet passend zijn dat er sprake is van dreigend ziekteverzuim. Welke aanpassingen in de werkzaamheden of op de werkplek zijn mogelijk om in het werkproces te blijven?
- er sprake is van ziekteverzuim door medische belemmeringen en iemand zich niet in staat acht om te werken of iemand juist weer aan het werk wil.
- er behoefte is aan bedrijfsartsgeneeskundige expertise om op het werk (de gevolgen van) de medische beperkingen te bespreken.

Wijs de (zelfstandig) werkende of werkzoekende patiënt op de website c-support.nu. Deze site bevat veel informatie over werkgerelateerde vragen na COVID-19.

Voor de bedrijfs- of verzekeringsarts

Overweeg gebruik te maken van de adviezen over de inventarisatie van de problematiek/belemmerende factoren, inventarisatie van het herstelgedrag en het opstellen van een re-integratieadvies, zoals beschreven in de richtlijn 'Chronisch Ziekten en Werk' en de Multidisciplinaire LCI-richtlijn Q-koortsvermoeidheidssyndroom'.

Overwegingen

Het Nederlands Centrum voor Beroepsziekten (NCvB) registreert en signaleert jaarlijks beroepsziekten (Kerncijfers beroepsziekten, 2021). De Kerncijfers beroepsziekten 2021 geven enig inzicht in de mate van verzuim bij COVID-19 als beroepsziekte. Uit deze cijfers blijkt dat de incidentie van beroepsziekten in 2020 is gestegen naar 243 (95%-BI 229-258) per 100.000 werknemers in 2020. Dit cijfer is substantieel hoger dan de voorgaande jaren, toen de incidentie varieerde van 121-191 per 100.000 werknemers. In 2020 zijn er bij het NCvB 1918 meldingen gedaan van COVID-19 als beroepsziekte. De meeste COVID-19-meldingen als beroepsziekte zijn afkomstig uit de gezondheidszorg. Uit de verzuimduur van deze meldingen blijkt dat 44% < 1 maand verzuimt (waarschijnlijk de isolatieperiode), in 30% van de gevallen is de verzuimperiode tussen 1 en 3 maanden, in 18% van de gevallen is de verzuimduur 3-6 maanden en 8% verzuimt > 6 maanden. De kans

op spontaan herstel, en daardoor terugkeer naar werk, < 6 maanden na COVID-19 is dus > 90%. Hierbij geldt wel de kanttekening dat informatie over het totaal aantal positief geteste medewerkers ontbreekt en dit alleen over medewerkers gaat die geregistreerd zijn door een bedrijfsarts en bij wie er al minstens een paar weken sprake was van medische beperkingen. Een eventuele onderrapportage van beroepsziekten door bedrijfsartsen kan hierbij ook nog van invloed zijn op de genoemde cijfers.

De bedrijfs- of verzekeringsarts die een werk(zoek)ende met langdurige klachten na COVID-19 ziet, kan de richtlijn 'Chronisch Zieken en Werk' en/of de multidisciplinaire LCI-richtlijn 'Q-koortsvermoeidheidssyndroom' raadplegen voor informatie over de terugkeer naar werk. Hoewel beide richtlijnen de suggestie wekken zich alleen te richten op blijvende/chronische beperkingen door onder andere vermoeidheid, is dat niet juist. Beide richtlijnen richten zich op het hele palet van klachten, variërend van mentaal en fysiek tot sociaal-maatschappelijk participeren in de brede zin van het woord. De richtlijnen bevatten adviezen die de bedrijfs-/verzekeringsarts kunnen helpen bij de begeleiding van werk(zoek)enden. Hierbij gaat het om een inventarisatie van de medische beperkingen, de bevorderende en belemmerende factoren en het herstelgedrag, en het opstellen van een re-integratieadvies. Hierbij geldt wel de kanttekening dat bij langdurige klachten na COVID-19 het vaak een mengbeeld is van overbelasting, systeemproblematiek en klachten gerelateerd aan COVID-19, iedere beeld met zijn eigen natuurlijk beloop.

In mei 2021 is de eerste versie van de dynamische Leidraad 'Herstel & Re-integratie in het kielzog van COVID-19; Post-Acute gevolgen van SARS CoV-2 infectie (PASC)' van de Nederlandse Vereniging voor Arbeids- en Bedrijfsgeneeskunde verschenen. Naarmate er meer kennis beschikbaar komt, wordt het document aangepast. Interventies over terugkeer naar werk worden in een volgende versie uitgewerkt.

Zorgprofessionals kunnen een beroep doen op C-support ter ondersteuning of advisering.

Onderbouwing

Achtergrond

Een deel van de patiënten met doorgemaakte COVID-19 houdt langdurig klachten. Veelvoorkomende klachten die ≥ 4 weken aanhouden, zijn vermoeidheid, spiermassaverlies/spierzwakte, dyspneu, cognitieve stoornissen en verlies van reuk en/of smaak. Patiënten met langdurige klachten na COVID-19 kunnen naast fysieke en mentale klachten ook negatieve psychosociale en sociaal-emotionele gevolgen ondervinden. Dit kan samen met de fysieke en mentale klachten leiden tot een langere verzuimduur en stagnerende re-integratie.

Conclusies / Summary of Findings

- Results from four studies indicate that on average >85% of patients had returned to their previous work at three months follow up (quality of evidence: low).
- We are very uncertain about the prevalence of impairment at work due to health problems (quality of evidence: very low).
- We found no study that reported on hindering and promoting factors for return to work.

Samenvatting literatuur

One study was found and included in this summary of literature (Jacobson, 2021). The search update yielded a systematic review about the long-term impact of COVID-19 on patients ability to return to work, in which three additional studies were included (Sanchez, 2021). The search update yielded also one additional cohort study (Huang, 2021).

Description of the study

Garrigues (2020) assessed the prevalence of persistent symptoms > 100 days after hospitalization for COVID-19 by a short phone questionnaire (n=120; France; 100% hospitalized).

Liang (2020) aimed to assess persistent symptoms of COVID-19 patients 3 months after discharge by interview with a standardized questionnaire (n=76; China; 100% hospitalized).

Zhao (2020) studied the pulmonary function in COVID-19 patients 3 months after discharge (n=55; China; 100% hospitalized).

Jacobsen (2021) assessed the prevalence of persistent functional impairment after COVID-19 with a symptom survey, work productivity and activity index questionnaire, and 6-minute walk test, 3-4 months after initial COVID-19 diagnosis (n=118; United States; 19% hospitalized).

Huang (2021) described the health consequences between 6 and 12 months and work status at 12 months after COVID-19 (n=1276; China; 100% hospitalized; 68% had at least one sequelae symptom at 6 months).

Results

Return to work

Garrigues (2020) reported that 38 (68%) had gone back to work at 3-months after discharge.

Liang (2020) reported that 69 (91%) patients had returned to their original work at 3-months after discharge.

Zhao (2020) reported that all 55 patients had returned to their original work.

Jacobsen (2021) reported that 9 (12%) of currently employed patients missed work due to health problems in the past 7 days.

Huang (2021) reported that 422 (88%) of patients who were employed before COVID-19 had returned to their original work at 12 months.

Work productivity

Jacobsen (2021) reported that 39% (28/72) reported impairment at work due to health problems in the past 7 days.

Barriers and facilitators for return to work

We found no study that reported on hindering and promoting factors for return to work.

Zoeken en selecteren

Clinical questions

- What are the effects of persistent symptoms beyond 4 weeks from the onset of COVID-19 on participation at work (and/or study)?
- Can we identify barriers and facilitators for return to work?
- Which actions are recommended to healthcare professionals to promote return to work in patients ≥ 4 weeks of persistent symptoms after COVID-19?

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 17-5-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies answering at least one of the clinical questions were selected. The Appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion. The search was updated on September 3rd 2021.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Sick leave: as determined as paid time off of work due to illness.
- Work productivity: as measured with the Work productivity and impairment questionnaire (WPAI), the Work Ability Index (WAI), or the Treatment Inventory of Costs in Patients with psychiatric disorders (TIC-P, part II: questions about work).
- Barriers and facilitators for return to work

The working group did not predefine the outcome measure return to work, but used the definitions used in the included studies.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

<https://www.c-support.nu/werkwijzer/>

Jacobson KB, Rao M, Bonilla H, Subramanian A, Hack I, Madrigal M, Singh U, Jagannathan P, Grant P. Patients With Uncomplicated Coronavirus Disease 2019 (COVID-19) Have Long-Term Persistent Symptoms and Functional Impairment Similar to Patients with Severe COVID-19: A Cautionary Tale During a Global Pandemic. Clin Infect Dis. 2021 Aug 2;73(3):e826-e829. doi: 10.1093/cid/ciab103. PMID: 33624010; PMCID: PMC7929039.

Kerncijfers beroepsziekten 2021. Amsterdam: Nederlands Centrum voor Beroepsziekten, 2021.

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Richtlijn Chronisch Ziekten en Werk. Amsterdam: Coronel instituut voor arbeid en gezondheid, Academisch Medisch Centrum

(AMC), 2016.

Sanchez-Ramirez DC, Normand K, Zhaoyun Y, Torres-Castro R. Long-term impact of COVID-19: a systematic review of the literature and meta-analysis. *Biomedicines* 2021;9:900. DOI: 10.3390/biomedicines9080900. PMID: 34440104. PMCID: PMC8389585.

Medicamenteuze behandeling na COVID-19

Uitgangsvraag

Welke medicamenteuze behandelopties zijn aan te bevelen bij patiënten met aanhoudende klachten anders dan reuk- of smaakstoornissen ≥ 4 weken na COVID-19?

Aanbeveling

We bevelen medicamenteuze therapie (systemische corticosteroïden, inhalatiemedicatie, antitrombotica, pijnstillers, antifibrotische medicatie, vitaminesuppletie) of COVID-19 vaccinatie niet aan voor de bevordering van het herstel bij patiënten met langdurige klachten na COVID-19.

Overweeg het symptoom pijn te behandelen volgens de geldende richtlijnen.

Overwegingen

Voor- en nadelen van de interventie

Het is onbekend of medicamenteuze therapie effectief is voor de bevordering van het herstel bij patiënten die na COVID-19 ≥ 4 weken aanhoudende klachten hebben. Medicamenteuze therapie kan echter wel bijwerkingen geven.

Kwaliteit van bewijs

Er zijn geen onderzoeken beschikbaar over het effect van medicamenteuze therapie op het herstel bij patiënten met langdurige klachten na COVID-19.

Waarden en voorkeuren van patiënten

De meeste patiënten hebben waarschijnlijk geen voorkeur voor een medicamenteuze behandeling waarvan de effectiviteit niet is aangetoond en er een kans op bijwerkingen bestaat.

Kosten

De kosten zijn afhankelijk van de gekozen medicamenteuze behandeling.

Aanvaardbaarheid

Medicamenteuze therapie is voor de meeste patiënten waarschijnlijk geen aanvaardbare behandeling, omdat de effectiviteit niet is aangetoond.

Haalbaarheid

De werkgroep verwacht voor de meeste medicamenteuze behandelopties geen haalbaarheidsproblemen.

Waarom deze aanbeveling/rationale?

Er is geen wetenschappelijk bewijs voor de effectiviteit van medicamenteuze therapie (systemische corticosteroïden, inhalatiemedicatie, antitrombotica, pijnstillers, antifibrotische medicatie, vitaminesuppletie) op het bevorderen van herstel bij patiënten met langdurige klachten na COVID-19. Het is ook onbekend of

COVID-19-vaccinatie enig effect heeft op de bevordering van het herstel. Om deze reden bevelen we medicamenteuze therapie of een COVID-19-vaccinatie voor de bevordering van het herstel niet aan bij patiënten met aanhoudende klachten na COVID-19.

Onderbouwing

Achtergrond

Een deel van de patiënten met doorgemaakte COVID-19 houdt langdurig klachten (≥ 4 weken na COVID-19). Veelvoorkomende klachten die ≥ 4 weken aanhouden zijn kortademigheid, vermoeidheid, hoesten, slaapstoornissen, keelpijn, cognitieve stoornissen en verlies van reuk en/of smaak. Het is onduidelijk of er onderzoek gedaan is naar de rol van medicamenteuze therapie bij het herstel van aanhoudende klachten na COVID-19. Omdat sommige patiënten met aanhoudende klachten minder klachten ervaren na een COVID-19-vaccinatie, hebben we ook COVID-19-vaccinatie als medicamenteuze behandeloptie meegenomen.

Conclusies / Summary of Findings

We found no original research for any type of pharmacological therapy or COVID-19 vaccination in chronic/post-COVID-19 patients.

Zoeken en selecteren

Clinical question

Which drug treatment options are recommended in the recovery process of people with ongoing symptoms other than smell or taste disorders ≥ 4 weeks after COVID-19?

PICO

P: Adults who are experiencing ongoing symptoms 4 weeks from onset of COVID-19

I: Systemic steroids, inhalating agents (salbutamol, steroids), antithrombotic drugs (anticoagulants, antiplatelet drugs), pain relievers (paracetamol, NSAIDs), vitamins/supplements (vitamin C, vitamin D), antifibrotic agents (nintedanib, pirfenidone), COVID-19 vaccine

C: Usual care / no pharmacological therapy

O: Physical functioning (crucial), thrombo-embolic events (crucial; venous thrombo-embolism, pulmonary embolism, deep venous thrombosis, ischemic stroke, acute coronary syndrome), subjective dyspnea perception (important), pulmonary function (important), fatigue (important)

Other selection criteria

Study design: systematic reviews, RCTs. Follow-up: not specified

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 12-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO. The appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion. The search was updated on September 3rd 2021.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Physical functioning: as determined with a validated physical performance test (e.g. the Short Physical Performance Battery, Barthel Index).
- Subjective dyspnea perception: as assessed with the Basal Dyspnea Index and Visual Analog Scale
- Lung function: as determined with spirometry. Spirometry measures two key factors: expiratory forced vital capacity (FVC) and forced expiratory volume in one second (FEV1). The FEV1/FVC ratio is used to determine the diagnosis of obstructive and/or restrictive lung disease.
- Fatigue: as assessed with a validated fatigue questionnaire (e.g. Fatigue Severity Scale, Modified Fatigue Impact Scale).

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Behandeling reuk- en smaakstoornissen na COVID-19

Veel patiënten ervaren reukverlies tijdens COVID-19. Het merendeel (> 90%) herstelt hiervan < 1 maand. Bij ongeveer 6-8% procent van de patiënten persisteert het reukverlies echter. In deze richtlijn bespreken we of er aan te raden behandelingsstrategieën zijn in de vorm van medicatie (corticosteroïd oraal of in neusspray), reuktraining of counseling. Reuktraining is het dagelijks trainen van het reukvermogen door te ruiken aan 4 verschillende etherische oliën: roos, eucalyptus, citroen (limoen) en kruidnagel. Onduidelijk is wat de effectiviteit is van corticosteroïden (oraal of nasaal) of reuktraining bij patiënten met aanhoudende reuk- of smaakklachten na COVID-19.

Deze module is onderverdeeld in de volgende submodules:

- Behandeling met corticosteroïden
- Reuktraining

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Corticosteroïden na COVID-19

Uitgangsvraag

Is een behandeling met corticosteroïden systemisch en/of nasaal met of zonder reuktraining aan te bevelen bij patiënten die ≥ 4 weken na COVID-19 aanhoudende reuk- of smaakklachten hebben?

Aanbeveling

We bevelen corticosteroïden (systemisch of nasaal) niet aan bij patiënten met doorgemaakte COVID-19 en persisterend reukverlies (≥ 4 weken).

Overwegingen

Voor- en nadelen van de interventie

Het is onduidelijk of (nasale of systemische) corticosteroïden de reukfunctie verbeteren bij patiënten met doorgemaakte COVID-19 en langdurig reukverlies.

Het pathofysiologisch mechanisme van reukverlies door COVID-19 is nog niet geheel bekend. Wel lijkt inflammatie van het reukepitheel en bulbus olfactorius een rol te spelen. Het is maar zeer de vraag of nasale corticosteroïden deze regio kunnen bereiken. Orale corticosteroïden kunnen de regio wel bereiken, maar kunnen bijwerkingen geven.

Kwaliteit van bewijs

De kwaliteit van het bewijs is zeer laag. Er is slechts 1 kleine open-label RCT die de effectiviteit van corticosteroïden onderzocht bij patiënten met doorgemaakte COVID-19 en langdurig reukverlies.

Waarden en voorkeuren van patiënten

De meeste patiënten zullen geen behandeling met (nasale of systemisch toegediende) corticosteroïden willen, omdat de effectiviteit niet is aangetoond en er een kans op bijwerkingen bestaat.

Kosten

De kosten voor nasale corticosteroïden zijn € 0,06 tot € 0,16 per dag (medicijnkosten.nl, geraadpleegd op 20-05-2021). De kosten voor prednison 40 mg zijn € 0,14 per dag.

Aanvaardbaarheid

Het gebruik van een corticosteroïd neusspray kost de patiënt weinig tijd en moeite en is daardoor een aanvaardbare behandeling. Systemisch toegediende corticosteroïden kunnen bijwerkingen geven.

Haalbaarheid

De werkgroep verwacht geen haalbaarheidsproblemen.

Waarom deze aanbeveling/rationale?

Het is onduidelijk of (nasale of systemische) corticosteroïden de reukfunctie verbeteren bij patiënten met doorgemaakte COVID-19 en langdurig reukverlies, vanwege het gebrek aan wetenschappelijk bewijs. Op basis van het werkingsmechanisme is de werkgroep van mening dat nasaal toegediende steroïden niet

aangeraden moeten worden. Systemisch toegediende corticosteroïden kunnen bijwerkingen geven. Om deze reden bevelen we ook het gebruik van systemische corticosteroïden niet aan bij deze patiënten.

Onderbouwing

Achtergrond

Veel patiënten ervaren reukverlies tijdens COVID-19. Het merendeel (> 90%) herstelt hiervan < 1 maand. Bij ongeveer 6-8% procent van de patiënten persisteert het reukverlies echter. In deze richtlijn bespreken we of er aan te raden behandelingsstrategieën zijn in de vorm van medicatie (corticosteroïd oraal of in neusspray), reuktraining of counseling. Reuktraining is het dagelijks trainen van het reukvermogen door te ruiken aan 4 verschillende etherische oliën: roos, eucalyptus, citroen (limoen) en kruidnagel. Onduidelijk is wat de effectiviteit is van corticosteroïden (oraal of nasaal) of reuktraining bij patiënten met aanhoudende reuk- of smaakklachten na COVID-19.

Conclusies / Summary of Findings

- We are unsure whether a combination of systemic and nasal steroids improve olfactory function in patients with persisting anosmia ≥ 4 weeks after COVID-19 (certainty of evidence: very low)
- No studies reported on subjective olfactory function or quality of life.
- We found no studies that investigated the effects of either systemic or nasal steroids separately in patients with long COVID anosmia.

Samenvatting literatuur

Two systematic reviews were found that met the criteria for inclusion in this summary of literature (Kang, 2020; Addison 2021). However, they reported that no original research was found for oral and intranasal corticosteroids post-COVID-19 olfactory dysfunction. In addition, one RCT was found and included in the analysis of the literature (Vaira 2021); results are summarized in the evidence table. The assessment of the risk of bias is summarized in the risk of bias tables.

The search update yielded one living systematic review (Cochrane review) about interventions for the treatment of persistent post-COVID-19 olfactory dysfunction (O'Byrne, 2021). The only included study was Vaira (2021).

Description of studies

Vaira (2021) aimed to evaluate the efficacy of corticosteroids (systemic and nasal) in patients with COVID-19 related anosmia for more than 30 days. Patients were randomized to corticosteroids (systemic prednisone, starting with 1 mg/kg/day and tapering the dose, for 15 days and nasal irrigation with betamethasone, ambroxol, and rinazine for 15 days) or no treatment. 18 patients underwent randomization; 9 received corticosteroids and 9 received no treatment. All 18 patients completed the study (Italy; mean age 42 years; 39% men). Follow-up: 40 days.

Results

Table 1 shows the summary of findings for the various outcome measures. More detailed information on the outcomes can be found below.

SoF table 1. Systemic and nasal corticosteroid therapy versus no treatment for persistent anosmia post-COVID-19 anosmia

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		No treatment	Corticosteroids		
Recovery ¹ 40 days	Relative risk: 11.0 –CI 95% 0.7 - 173.66) Based on data from 18 patients in 1 studies Follow up 40 days [Vaira 2021]	0 per 1000	556 per 1000 Difference: 556 more per 1000 (CI 95–% 219 more - 892 more)	Very low door ernstige risico op bias, door zeer ernstige onnauwkeurigheid ²	We are unsure about the effect of corticosteroids on recovery of the sense of smell.
Olfactory function 20 days	Measured by: CCCRC Scale: 0 – 100 High better Based on data from 18 patients in 1 studies Follow up 40 days [Vaira 2021]	30 Median	70 Median Difference: 40 higher	Very low door ernstige risico op bias, door zeer ernstige onnauwkeurigheid ³	We are unsure whether corticosteroids improve olfactory function.
Olfactory function 40 days	Measured by: CCCRC Scale: 0 - 100 High better Based on data from 18 patients in 1 studies Follow up 40 days [Vaira 2021]	60 Median	90 Median Difference: 30 higher	Very low door ernstige risico op bias, door zeer ernstige onnauwkeurigheid ⁴	We are unsure whether corticosteroids improve olfactory function.
Olfactory function (subjective)					No studies reported on this outcome.
Quality of life					No studies reported on this outcome.

Adverse events	Based on data from 18 patients in 1 studies Follow up 40 days [Vaira 2021]	Vaira 2021: No patient developed any adverse events	Very low door ernstige risico op bias, door zeer ernstige onnauwkeurigheid ⁴	We are unsure whether corticosteroids have adverse events.

1. Assessed with: CCCRC test score (range 0 to 100, normal olfactory function classed as a score of 90 or 100)
2. **Risk of Bias: serious.** No blinding of participants.; **Imprecision: very serious.** Data from one small RCT. Large confidence intervals.;
3. **Risk of Bias: serious.** No blinding of participants.; **Imprecision: very serious.** Data from one small RCT. Large confidence intervals.;
4. **Risk of Bias: serious.** No blinding of participants.; **Imprecision: very serious.** Data from one small RCT. Large confidence intervals.;

Olfactory function

Vaira (2021) examined the olfactory function with the Connecticut Chemosensory Clinical Research Center (CCCRC) composite score. This composite score allows to classify the olfactory function of patients in normal (score 90 and 100), mild hyposmia (score 70 and 80), moderate hyposmia (score 50 and 60), severe hyposmia (score between 20 and 40) and anosmia (score 0 and 10). Patients in the corticosteroid (systemic and nasal) group reported significantly higher improvements of the olfactory scores than the controls at both the 20-day [40 (IQR 45) versus 10 (IQR 15); $p = 0.011$] and 40-day [60 (IQR 40) versus 30 (IQR 25); $p = 0.024$] evaluations.

Recovery of sense of smell

Vaira (2021) examined the olfactory function with the CCCRC score. A score of ≥ 90 represents normal olfactory function. The evidence is very uncertain about the effect of this intervention on recovery of the sense of smell at 40 days: 5/9 participants in the intervention group scored ≥ 90 compared to 0/9 in the control group.

Subjective olfactory function

No studies reported on subjective olfactory function.

Quality of life

No studies reported on quality of life.

Adverse events

Vaira (2021) reported that no patient developed any adverse events. However, did not identify any participants of this study; however, it is unclear how these outcomes were assessed and recorded.

Zoeken en selecteren

Clinical question

Is steroid therapy (nasal and/or systemic) with/without smell training helpful in the recovery process of people with ongoing smell/taste disorders ≥ 4 weeks after COVID-19?

PICO

P: Adults who are experiencing ongoing smell/taste disorders ≥ 4 weeks from onset of COVID-19

I: Corticosteroid therapy (nasal and/or systemic) with or without olfactory training

C: Placebo / no therapy / olfactory training only

O: Olfactory function (crucial), adverse events (crucial), subjective olfactory function (important; VAS), recovery (important), quality of life (important)

Other selection criteria

Study design: systematic reviews, RCTs. Follow-up: not specified

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 30-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). The systematic literature search resulted in 122 hits. Studies were selected based on the criteria as described in the PICO. Only systematic reviews and randomized controlled trials (RCTs) were included. Seven studies were initially selected based on title and abstract screening. After reading the full text, 4 studies were excluded (see the [PRISMA flowchart](#) in the appendices (*Bijlagen*) and the table with reasons for exclusion in the evidence tables (*Evidence tabellen*)), and three studies were included. The search was updated on September 3rd 2021.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Olfactory function as determined with validated olfactory tests (e.g. Sniffin' Sticks test, University of Pennsylvania Smell Identification Test or Connecticut chemosensory clinical research center test).
- Subjective olfactory function as determined with a visual analogue scale (VAS).
- Quality of life as determined with a validated questionnaire (e.g. EQ-5D-5L).

The working group defined 5.5 points on the TDI score (composite score from Sniffin' Stick test) (Gudziol, 2006) as minimal clinically (patient) important difference. For all other continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

[Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, et al. Clinical Olfactory Working Group consensus](#)

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Reuktraining na COVID-19

Uitgangsvraag

Is een behandeling met reuktraining aan te bevelen bij patiënten die ≥ 4 weken na COVID-19 aanhoudende reuk- of smaakklachten hebben?

Aanbeveling

Bespreek de mogelijkheid van reuktraining bij patiënten die 4 weken na COVID-19 nog een reukstoornis hebben. Verwijzing naar een KNO-arts voor reuktraining is niet nodig.

Bij keuze voor reuktraining: adviseer de training tweemaal per dag uit te voeren gedurende tenminste 3-6 maanden.

Overwegingen

Voor- en nadelen van de interventie

We hebben geen onderzoeken gevonden over de effectiviteit van reuktraining bij patiënten met doorgemaakte COVID-19.

Uit onderzoek bij andere postvirale infecties met reukverlies blijkt dat reuktraining mogelijk het reukherstel bespoedigt en vergroot (Kattar 2021). De therapie is niet invasief en weinig belastend. Om resultaat te bereiken, moet de patiënt de reuktraining tweemaal per dag doen gedurende tenminste 3-6 maanden. Indien de training na 3 maanden nog geen of onvoldoende effect heeft, dient de patiënt op een nieuwe set geuren over te stappen voor de volgende 3 maanden.

Kwaliteit van bewijs

Er is geen wetenschappelijk bewijs voor de effectiviteit van reuktraining bij post-COVID-19-patiënten met langdurig reukverlies; bij andere postvirale infecties met reukverlies is de bewijskracht voor reukherstel door reuktraining laag.

Waarden en voorkeuren van patiënten

De motivatie van patiënten is voor deze behandeling naar verwachting groot.

Kosten

De kosten bedragen € 25-50. De kosten zijn € 25 per set (inhoud: 4 etherische oliën). Na 3 maanden dient de patiënt over te stappen op een andere set geuren indien er nog onvoldoende effect is opgetreden.

Aanvaardbaarheid

Reuktraining kost de patiënt weinig tijd en moeite, geeft geen bijwerkingen en is daardoor een aanvaardbare behandeling.

Haalbaarheid

De werkgroep verwacht geen haalbaarheidsproblemen.

Waarom deze aanbeveling/rationale?

Er is geen wetenschappelijk bewijs voor de effectiviteit van reuktraining bij patiënten met doorgemaakte COVID-19 en langdurig reukverlies. Bij andere postvirale infecties met reukverlies bespoedigt en vergroot reuktraining mogelijk het reukherstel. Omdat reuktraining mogelijk helpt in het herstelproces en geen bijwerkingen kent, doen we een zwakke aanbeveling voor reuktraining bij deze patiënten.

Onderbouwing

Achtergrond

Veel patiënten ervaren reukverlies tijdens COVID-19. Het merendeel (> 90%) herstelt hiervan < 1 maand. Bij ongeveer 6-8% procent van de patiënten persisteert het reukverlies echter. In deze richtlijn bespreken we of er aan te raden behandelingsstrategieën zijn in de vorm van medicatie (corticosteroïd oraal of in neusspray), reuktraining of counseling. Reuktraining is het dagelijks trainen van het reukvermogen door te ruiken aan 4 verschillende etherische oliën: roos, eucalyptus, citroen (limoen) en kruidnagel. Onduidelijk is wat de effectiviteit is van corticosteroïden (oraal of nasaal) of reuktraining bij patiënten met aanhoudende reuk- of smaakklachten na COVID-19.

Conclusies / Summary of Findings

- We found no studies that investigated the efficacy of olfactory training specifically for post COVID-19 olfactory dysfunction.
- Olfactory training may improve (subjective) olfactory function in patients with postinfectious olfactory dysfunction (certainty of evidence: low)
- No studies reported on quality of life.

Samenvatting literatuur

Two systematic reviews were found that met the criteria for inclusion in this summary of literature (Kang, 2020; Addison, 2021). The search update yielded one living systematic review (Cochrane review) about interventions for the treatment of persistent post-COVID-19 olfactory dysfunction (O'Byrne, 2021). However, they found no original research for olfactory training (OT) specifically for post COVID-19 olfactory dysfunction.

As none of the studies fulfilled all pre-specified criteria, we decided to describe studies that evaluated the efficacy of OT for specifically postinfectious olfactory dysfunction (PIOD)(Kattar 2021). Two RCTs were found and included in the analysis of the literature; results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Description of studies

Damm (2014) aimed to evaluate the efficacy of OT in patients with persistent PIOD for at least 8 weeks. Patients were randomized to OT with either high or low odorant concentrations for 18 weeks. 144 of the 171 randomized patients completed the second visit at week 16-18 (Germany; mean age 55 years; 37% men; mean duration PIOD 10.5 months). Follow-up: 18 and 36 weeks.

Altundag (2015) aimed to evaluate the efficacy of OT in patients with persistent PIOD referred to the Department of Otorhinolaryngology of Istanbul Surgery Hospital. Patients were randomized to modified OT,

classical OT or no treatment. All 48 patients randomized patients (classical OT or control group) completed the study (Turkey; mean age 46 years; 47% men; mean duration PIOD 7.0 months).
Follow-up: 12, 24 and 36 weeks.

Results

Table 2 shows the summary of findings for the various outcome measures. More detailed information on the outcomes can be found below.

SoF table 2. Olfactory training versus no treatment for postinfectious olfactory dysfunction

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain text summary
		No olfactory training	Olfactory training		
Improvement of olfactory function ¹ (12-18 weeks)	Relative risk: 2.05 (CI 95% 1.06 - 3.97) Based on data from 192 patients in 2 studies Follow up 12-18 weeks	114 per 1000	247 per 1000	Low door ernstige risico op bias, door ernstige onnauwkeurigheid ²	Olfactory training may improve olfactory function.
		Difference: 133 more per 1000 (CI 95% 25 more - 240 more)			
Subjective olfactory function (12 weeks)	Measured by: VAS Scale: 1 - 10 High better Based on data from 48 patients in 1 studies Follow up 12 weeks	2.7 Mean	4.1 Mean	Low door ernstige risico op bias, door ernstige onnauwkeurigheid ³	Olfactory training may improve subjective olfactory function.
		Difference: MD 1.40 higher (CI 95% 0.69 higher - 2.11 higher)			

1. Improvement of TDI scores of at least six points (maximum score is 48)
2. **Risk of Bias: Serious. Unclear randomisation Imprecision: Serious.**
3. **Risk of Bias: Serious. Unclear randomisation; Imprecision: Serious.** Only 1 small study

Olfactory function

Damm (2014) examined the improvement in olfactory function (change in the TDI score ≥ 6). At 18 weeks, olfactory function improved in the high-training group in 18 of 70 participants (25.7%), whereas only 11 of 74 improved in the low-training group (14.9%).

Altundag (2015) examined the improvement in olfactory function (change in the TDI score ≥ 6). At 12 weeks, olfactory function improved in the classical OT group in 7 of 33 participants (21%), whereas none improved in the control group.

Subjective olfactory function

Altundag (2015) examined the subjective olfactory function on visual analogue scales ranging from 1 to 10, with 10 indicating excellent olfactory function. Patients in the classical OT reported significant higher olfactory

function than patients in the control group [4.1 versus 2.7, mean difference 1.4; 95%CI 0.7-2.1].

Quality of life

No studies reported on quality of life.

Zoeken en selecteren

Clinical question

Is olfactory training helpful in the recovery process of people with smell/taste disorders ≥ 4 weeks after COVID-19?

PICO

P: Adults who are experiencing ongoing smell/taste disorders ≥ 4 weeks from onset of COVID-19

I: Olfactory training

C: No therapy

O: Olfactory function (crucial), subjective olfactory function (important; VAS), recovery (important), quality of life (important)

Other selection criteria

Study design: systematic reviews, RCTs. Follow-up: not specified

The databases [Medline (via OVID) and Embase (via Embase.com)] were searched with relevant search terms from 2020 until 30-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). The systematic literature search resulted in 122 hits. Studies were selected based on the criteria as described in the PICO. Only systematic reviews and randomized controlled trials (RCTs) were included. Seven studies were initially selected based on title and abstract screening. After reading the full text, five studies were excluded (see the [PRISMA flowchart](#) in the appendices (*Bijlagen*) and the table with reasons for exclusion in the Evidence tables (*Evidence tabellen*), and two studies were included. The search was updated on September 3rd 2021.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Olfactory function as determined with validated olfactory tests (e.g. Sniffin' Sticks test, University of Pennsylvania Smell Identification Test or Connecticut chemosensory clinical research center test).
- Subjective olfactory function as determined with a visual analogue scale (VAS).
- Quality of life as determined with a validated questionnaire (e.g. EQ-5D-5L).

The working group defined 5.5 points on the TDI score (composite score from Sniffin' Stick test) (Gudziol, 2006) as minimal clinically (patient) important difference. For all other continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

- Addison AB, Wong B, Ahmed T, Macchi A, Konstantinidis I, Huart C, et al. Clinical Olfactory Working Group consensus statement on the treatment of postinfectious olfactory dysfunction. *J Allergy Clin Immunol* 2021;147:1704-19. DOI: 10.1016/j.jaci.2020.12.641. Epub 2021 Jan 13. PMID: 33453291.
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Voedingsinterventies na COVID-19

Uitgangsvraag

Welke voedingsinterventie kunnen we aanbevelen bij patiënten die risico lopen op spiermassaverlies ≥ 4 weken na COVID-19?

Aanbeveling

Voorlichting

- Leg uit bij patiënten met risico op spiermassaverlies dat spiermassaverlies snel optreedt, maar langzaam herstelt zonder aanvullende maatregelen op het gebied van voeding en bewegen.
- Geef informatie over de gevolgen van spiermassaverlies en het belang van goede voeding.
- Adviseer eiwitrijke voeding en extra eetmomenten (6 x per dag) en adviseer om dit met bewegen te combineren. Evalueer na 2 weken de eiwitinname en voortuitgang ten aanzien van spierzwakte.
- We bevelen het gebruik van voedingssupplementen niet aan (zie de module Medicamenteuze behandeling).
- Verwijs zo nodig naar Thuisarts.nl (<https://www.thuisarts.nl/mager-geworden/ik-ben-te-veel-afgevalen-en-wil-weer-sterker-worden>).

Verwijzing

- Zet bij patiënten bij wie in het ziekenhuis al een indicatie voor een voedingsinterventie was gesteld deze behandeling door de diëtist voort.
- Verwijs naar de diëtist bij evident onvoldoende eiwitinname wanneer een algemeen voedingsadvies niet toereikend is (geweest).
- Verwijs patiënten ook naar de diëtist bij onvoldoende herstel van de spierzwakte. In dit geval heeft een gecombineerde voedings- en beweeginterventie door de fysiotherapeut de voorkeur. De noodzaak voor deze gecombineerde interventie geldt zeker bij ouderen.

Overwegingen

Voor- en nadelen van de interventie

Er is geen wetenschappelijk onderzoek gedaan naar voeding/dieetadviezen bij patiënten met langdurige klachten na COVID-19. Resultaten van het COVOED-onderzoek laten zien dat de prevalentie van voedingsgerelateerde klachten hoog is onder COVID-19-patiënten die in het ziekenhuis opgenomen zijn geweest. Goede, eiwitrijke voeding kan in combinatie met beweging zorgen voor opbouw van spiermassa en preventie van verlies van spiermassa bij ziekte, slechte voedingsinname en inactiviteit. Helaas is er nog geen onderzoek gedaan naar de invloed van voedingsinterventies bij patiënten met langdurige klachten na COVID-19.

Kwaliteit van bewijs

Er zijn geen onderzoeken beschikbaar over het effect van voedingsinterventies bij patiënten met langdurige klachten na COVID-19.

Waarden en voorkeuren van patiënten

De werkgroep schat in dat patiënten met langdurige klachten na COVID-19 graag hulp willen om zich beter te voelen en beter te herstellen, en voedingsadviezen van de huisarts en/of diëtist daarom graag ter harte nemen.

Kosten

Algemeen voedingsadvies bij de huisarts valt, afhankelijk van de duur van het consult, onder de kosten van een enkel of dubbel consult (€ 10,51 of € 21,03).

Behandeling door een diëtist is opgenomen in de regeling Paramedische herstellzorg COVID-19 voor 7 uur voor een eerste behandeltermijn van 6 maanden. Indien nodig kan dit verlengd worden met nog een behandeltermijn van 6 maanden en dan nogmaals 7 uur.

Aanvaardbaarheid

Er zijn geen noemenswaardige bezwaren met betrekking tot de aanvaardbaarheid van het krijgen van een voedings-/dieetadvies.

Haalbaarheid

Elke (huis)arts is in staat om algemene voedingsadviezen te geven. Mocht dit onvoldoende zijn en/of als de (huis)arts zich hier niet bekwaam in voelt, dan kan de patiënt verwezen worden naar de diëtist. Een bezoek aan de diëtist of huisbezoek door de diëtist is relatief laagdrempelig, is vaak in de buurt bij de patiënt. Met goede begeleiding is het voor veel patiënten haalbaar om hun voedingspatroon aan te passen.

Waarom deze aanbeveling/rationale?

- Veel mensen met langdurige klachten na COVID-19, die thuis door ziekte meerdere dagen geen of nauwelijks beweging hebben gehad of in het ziekenhuis opgenomen zijn geweest, hebben een risico op ondervoeding en een verminderde spiermassa. Er zijn geen onderzoeken beschikbaar over het effect van voedingsinterventies bij patiënten met langdurige klachten na COVID-19.
- Dieetbehandeling kan, in combinatie met beweging, bijdragen aan een goed gewicht en een gunstige lichaamssamenstelling c.q. opbouw van spiermassa en verbetering van de voedingstoestand en functionaliteit

Onderbouwing

Achtergrond

Bij COVID-19 kunnen symptomen optreden die ondervoeding en sarcopenie in de hand werken. Uit het COVOED-onderzoek onder 407 COVID-19-patiënten opgenomen in 4 algemene en academische ziekenhuizen in Nederland, blijkt dat bijna de helft ondervoed was en bijna driekwart een hoog risico op spiermassaverlies had (Wierdsma, 2021). Verlies van gewicht en spiermassa blijkt veelvuldig voor te komen, zowel onder COVID-19-patiënten die in het ziekenhuis opgenomen zijn geweest als onder patiënten die thuis uitgezikt zijn (Di Filippo, 2021). Bij personen die voldoende eten en inactief zijn, is er een gevaar voor gewichtstoename en zelfs een afname van spiermassa in combinatie met gewichtstoename, waardoor het

spiermassaverlies gemaskeerd kan worden. Bij patiënten met spiermassaverlies zou een voedingsbehandeling moeten worden ingezet en worden voortgezet, ook na behandeling in het ziekenhuis. De LESA Ondervoeding geeft hiervoor handvaten (LESA Ondervoeding). Onduidelijk is of er onderzoek gedaan is naar voedingsinterventies ter preventie of behandeling van ondervoeding bij specifiek patiënten met doorgemaakte COVID-19.

Conclusies / Summary of Findings

We found no original research for any type of nutrition management in the chronic/post-COVID patients.

Samenvatting literatuur

Only one systematic review was found that met the criteria for inclusion in this summary of literature (Mechanick, 2020). However, they reported that no original research was found for nutrition risk assessment during outpatient follow-up; weight management (loss, maintenance, or gain) to improve recovery; the effect of targeted protein-energy goals on reducing risk of post-COVID-19 complications; the impact of registered dietitian nutritionist (RDN) counseling; energy expenditure and goal-directed nutrition therapy with prolonged critical illness and post-ICU care. No additional RCTs (published after the systematic review) were found.

Zoeken en selecteren

Clinical question

Which nutrition management is helpful in the recovery process of patients at risk for loss of muscle mass ≥ 4 weeks after COVID-19?

PICO

P: Adults at risk for loss of muscle mass ≥ 4 weeks after COVID-19

I: Any type of nutrition management

C: Usual care

O: Physical functioning (crucial), muscle mass (important), muscle strength (important), exercise intolerance (important), body weight (important), protein intake (important), quality of life (important)

Other selection criteria

Study design: systematic reviews, RCTs. Follow-up: not specified

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2020 until 12-4-2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO. The appendices (*Bijlagen*) contains the [PRISMA flowchart](#) showing the number of hits, and the reasons of exclusion. The search was updated on September 3rd 2021.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Physical functioning: as assessed by a validated performance questionnaire/test (e.g. the Short Physical Performance Battery, Barthel Index, 6 minute walk-test)

- Muscle mass: estimated by bioelectrical impedance analysis (BIA), whole-body DXA scans, computed tomography (CT) analysis or air displacement plethysmography.
- Muscle strength: as assessed by dynamometry.

The working group defined 5.0 to 6.5 kg as reasonable estimates of meaningful changes in grip strength measured with a hand dynamometer (Bohannon, 2019). For all other continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnen database.

Referenties

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Fysiek trainingsprogramma na COVID-19

Uitgangsvraag

Wat is de waarde van een fysiek trainingsprogramma bij patiënten die ≥ 4 weken geleden COVID-19 hebben doorgemaakt? En indien deze interventie wordt aangeraden, wat dient dan de vorm, frequentie, intensiteit en duur van het programma te zijn?

Aanbeveling

Overweeg oefen- of fysiotherapie bij patiënten met doorgemaakte COVID-19 die na ≥ 6 weken nog beperkingen ervaren in het dagelijks functioneren als gevolg van een verminderde inspanningstolerantie, vermoeidheid bij fysieke inspanning of dyspneu bij fysieke inspanning, balansproblemen en/of een verminderde spierkracht.

Voor oefen- en fysiotherapeuten

Bepaal samen met de patiënt het huidige en gewenste niveau van functioneren. Gebruik indien beschikbaar hierbij ook de gegevens uit de cardiopulmonary exercise test (CPET). Stel op basis hiervan een behandelplan op.

Monitor de belasting en belastbaarheid van de patiënt gedurende de training(speriode). Pas zo nodig de trainingsintensiteit aan en geef adviezen over de energieverdeling over de dag.

Zie ook de modules:

- Inspanningsdiagnostiek: voor adviezen over de indicaties voor een cardiopulmonary exercise test (CPET).
- Energiemanagement: voor adviezen over de indicaties voor verwijzing (via de huisarts of medisch specialist) naar een ergotherapeut voor begeleiding met betrekking tot energiemangement.
- Voedingsinterventies: voor adviezen over de indicaties voor verwijzing (via de huisarts of medisch specialist) naar een diëtist.

Overwegingen

Voor- en nadelen van de interventie

Ongeveer 10% van de patiënten na doorgemaakte COVID-19 rapporteert na 4 weken nog beperkingen in het dagelijks functioneren als gevolg van vermoeidheid, dyspneu bij fysieke inspanning, balansstoornissen en/of krachtsverlies (Greenhalgh, 2020). Op dit moment zijn er nog slechts een beperkt aantal onderzoeken beschikbaar waarin het effect van een fysiek trainingsprogramma is onderzocht. Er zijn aanwijzingen dat een ongesuperviseerd fysiek trainingsprogramma van 6 weken positieve effecten heeft bij patiënten na doorgemaakte COVID-19. Daarnaast zijn er aanwijzingen dat bij oudere mannen met sarcopenie na COVID-19 een trainingsprogramma van 8 weken met een lage intensiteit, gericht op het aerobe uithoudingsvermogen, gunstigere effecten heeft dan een hoogintensief programma. De kwaliteit van het bewijs is echter zeer laag en het is de vraag in hoeverre de resultaten van deze onderzoeken te generaliseren zijn naar de gehele populatie in Nederland.

Ondanks de beperkte wetenschappelijke onderbouwing verwacht de werkgroep dat de klachten na een SARS-CoV-2-infectie (gedeeltelijk) reversibel zijn, naar analogie van de kennis over trainingseffecten bij coronair lijden, COPD en oncologische aandoeningen met oefen- en fysiotherapie.

Het is belangrijk dat de oefen- of fysiotherapeut samen met de patiënt inventariseert wat het huidige en gewenste niveau van fysieke fitheid, functioneren en participatie is, en het trainingsprogramma hierop afstemt. Voor meer handvatten voor mogelijke meetinstrumenten verwijzen we naar de het KNGF-standpunt (KNGF, 2021). Bij sommige patiënten is een *cardiopulmonary exercise test* (CPET; maximaaltest) geïndiceerd om de belastbaarheid te bepalen en een verwijzing naar de ergotherapeut en/of diëtist gewenst. Zie de modules Inspanningsdiagnostiek, Energiemanagement en Voedingsinterventies voor de betreffende indicaties. Soms is het wenselijk om ook de sociale omgeving van de patiënt bij de interventie te betrekken.

Gezien de beperkte wetenschappelijke literatuur is het niet mogelijk om een specifiek trainingsprogramma of een specifieke dosering aan te raden. Op basis van FITT-principes (Frequentie, Intensiteit, Tijdsduur, Type) dient rekening te worden gehouden met de individuele belastbaarheid van de patiënt en wordt aangeraden om de balans tussen belasting en belastbaarheid regelmatig te evalueren. Hierbij is het belangrijk om ook aandacht te hebben voor het verdelen van energie in het geheel van de dagelijkse activiteiten van de patiënt. Overmatige vermoeidheid na inspanning (*post exertional malaise*) lijkt na COVID-19 een frequent voorkomend probleem. Hiernaast is de ervaring uit de praktijk dat er soms te intensief getraind werd/wordt, met overtraining als gevolg. De werkgroep acht het dan ook belangrijk dat gedurende de trainingsperiode geregeld wordt nagevraagd of er sprake is van overmatige vermoeidheid, benauwdheid, spierpijn en/of koorts tot 2 dagen na de training. Deze aspecten kunnen gemonitord worden met de Borgschaal (Borg, 1982; zie ook het KNGF-standpunt voor aanvullende adviezen over de inzet van de Borgschaal). Waar nodig kan de trainingsintensiteit aangepast worden en meer aandacht worden gegeven aan de energieverdeling. Desgewenst kan hierbij worden samengewerkt of afgestemd met een ergotherapeut (zie de module Energiemanagement).

Kwaliteit van bewijs

De bewijskracht voor de cruciale uitkomstmaten fysiek functioneren en kwaliteit van leven was laag. Door het ontbreken van data over de cruciale uitkomstmaat fysieke fitheid is de overkoepelende bewijskracht zeer laag. Hier ligt een kennislacune. De aanbevelingen zijn gebaseerd op aanvullende argumenten, waaronder expert opinie, waar mogelijk onderbouwd met (indirect) bewijs.

Waarden en voorkeuren van patiënten

Er is variatie in de voorkeuren van patiënten over een fysiek trainingsprogramma en over de vorm van een eventueel programma. Begeleiding in een oefenzaal is voor sommige patiënten belangrijk om grip te krijgen op de balans tussen belasting en belastbaarheid. Naast groepsbegeleiding hebben patiënten vaak behoefte hebben aan 1-op-1-begeleiding. Andere patiënten willen het programma juist graag thuis uitvoeren. De ruimte en tijd voor fysieke belasting wisselt ook per patiënt en hangt samen met de fysieke en/of emotionele belasting die thuis, op werk of in de sociale omgeving wordt ervaren. Het is belangrijk om deze voorkeuren te inventariseren en te respecteren.

Kosten

Oefen- en fysiotherapie maakt deel uit van de regeling Paramedisch herstelzorg (2021). De therapie wordt vergoed uit de basisverzekering (maar gaat wel ten koste van het eigen risico) indien de huisarts of medisch specialist de patiënt < 6 maanden na afloop van het acute infectiestadium verwijst. Indien de patiënt hier geen beroep op wil doen, wordt de therapie niet vergoed uit de basisverzekering. De regeling loopt vooralsnog tot augustus 2022.

Aanvaardbaarheid

Er worden geen problemen met betrekking tot de aanvaardbaarheid verwacht.

Haalbaarheid

Er worden geen problemen met betrekking tot de haalbaarheid verwacht.

Waarom deze aanbeveling/rationale?

De werkgroep verwacht op basis van ervaring dat met oefen- en fysiotherapie de ervaren beperkingen in het dagelijks functioneren als gevolg van vermoeidheid, dyspneu bij fysieke inspanning, balansstoornissen en/of krachtsverlies (gedeeltelijk) reversibel zijn. De werkgroep kiest daarom voor een zwakke positieve aanbeveling over de inzet van een fysiek trainingsprogramma. Er is gekozen voor een termijn van 6 weken na infectie omdat een deel van de patiënten tussen 4 en 6 weken nog spontaan herstelt.

Onderbouwing

Achtergrond

Patiënten kunnen na een doorgemaakte COVID-19 vermoeidheid en een verminderde belastbaarheid of verminderde fysieke fitheid ervaren (zie de module Natuurlijk beloop). Patiënten kunnen hun fysieke fitheid naar verwachting verbeteren met fysieke training. Mogelijk zorgt dit ook voor een vermindering van de vermoeidheidsklachten.

Conclusies / Summary of Findings

Summary of findings and conclusions are presented in tables 1 and 2. The critical outcome physical fitness and the important outcomes fatigue, physical activities and return to work were not reported in the included studies.

Samenvatting literatuur

Two RCTs were included in the analysis of the literature. Results and conclusions are summarized in the summary of findings tables (table 1 and 2).

Table 1. Summary of findings physical training versus no physical training

Population: recovering COVID-19 patients

Intervention: unsupervised 6-week home exercise program

Comparator: short educational instructions at baseline

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		control	exercise		
Physical functioning 28 weeks	Measured by: 6MWD Scale: - High better Based on data from 119 patients in 1 study ¹	15.17 % improvement from baselineMean	84.81 % improvement from baselineMean	Low Due to very serious imprecision and some concerns considering risk of bias ²	Exercise may improve physical functioning at 28- week follow-up
		Difference: MD 68.62 higher (CI 95% 46.39 higher - 90.85 higher)			
Physical functioning 6 weeks	Measured by: 6MWD Scale: - High better Based on data from 119 patients in 1 study ³	17.09 % improvement from baselineMean	80.20 % improvement from baselineMean	Low Due to very serious imprecision and some concerns considering risk of bias ⁴	Exercise may improve physical functioning at 6- week follow-up
		Difference: MD 65.45 higher (CI 95% 43.80 higher - 87.10 higher)			
Quality of life 28 weeks	Measured by: SF- 12 PCS Scale: - High better Based on data from 105 patients in 1 study ⁵ Follow up 28 weeks	5.20 Mean	8.2 Mean	Low Due to serious imprecision and serious risk of bias ⁶	Exercise may improve quality of life at 28-week follow-up
		Difference: MD 2.69 higher (CI 95% 0.06 higher - 5.32 higher)			
Quality of life 6 weeks	Measured by: SF- 12 PCS Scale: - High better Based on data from 112 patients in 1 study ⁷ Follow up 28 weeks	3.84 Mean	7.81 Mean	Low Due to serious imprecision and serious risk of bias ⁸	Exercise may improve quality of life at 6-week follow-up
		Difference: MD 3.79 higher (CI 95% 1.24 higher - 6.35 higher)			

Adverse events 6 weeks	Measured by: number of events Scale: - Lower better Based on data from 112 patients in 1 study ⁹ Follow up 28 weeks	0 Mean	0 Mean	Low Due to very serious imprecision and serious risk of bias ¹⁰	There were too few who experienced the adverse events, to determine whether exercise made a difference

6MWD: 6-minute walk test; SF-12 PCS: 12-item Short Form Health Survey-12; MD: mean difference; CI: confidence interval.

1. Primary study. **Baseline/comparator** Primary study. Supporting references [1].
2. **Imprecision: serious.** Low number of patients, Only data from one study; **Risk of bias: serious.** Lack of blinding
3. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Li, 2021].
4. **Imprecision: very serious.** Low number of patients, Only data from one study; **Risk of bias: serious.** Lack of blinding
5. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Li, 2021].
6. **Imprecision: very serious.** Low number of patients, Only data from one study; **Risk of bias: serious.** Lack of blinding
7. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Li, 2021].
8. **Imprecision: very serious.** Low number of patients, Only data from one study; **Risk of bias: serious.** Lack of blinding
9. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Li, 2021].
10. **Imprecision: very serious.** Low number of patients, Only data from one study; **Risk of bias: serious.** Lack of blinding

Table 2. Summary of findings physical low versus high intensity physical training

Population: Older men with post-COVID-19 sarcopenia

Intervention: High-intensity aerobic training for 8 weeks

Comparator: Low-intensity aerobic training for 8 weeks

Outcome Timeframe	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Low-intensity	High-intensity		
Quality of life 6 months	Measured by: SarQOL Scale: - High better Based on data from 69 patients in 1 study ¹	72.6 Mean	62.2 Mean	Low Due to very serious imprecision ²	Low-intensity aerobic training may improve quality of life compared to high-intensity training at 6-month follow-up
		Difference: MD 10.4 lower (CI 95% 9.97 lower - 10.83 lower)			
Quality of life 8 weeks	Measured by: SarQOL Scale: - High better Based on data from 73 patients in 1 study ³	69.0 Mean	60.5 Mean	Low Due to very serious imprecision ⁴	Low-intensity aerobic training may improve quality of life compared to high-intensity training at 8-week follow-up
		Difference: MD 8.50 lower (CI 95% 8.08 lower - 8.92 lower)			
Handgrip strength 6 months	Measured by: Hand dynamometer Scale: - High better Based on data from 69 patients in 1 study ⁵	34.3 kgMean	30.4 kgMean	Low Due to very serious imprecision ⁶	Low-intensity aerobic training may improve handgrip strength compared to high- intensity training at 6-month follow-up
		Difference: MD 3.90 lower (CI 95% 3.52 lower - 4.28 lower)			
Handgrip strength 8 weeks	Measured by: Hand dynamometer Scale: - High better Based on data from 73 patients in 1 study ⁷	31.5 kgMean	29.8 kgMean	Low Due to very serious imprecision ⁸	Low-intensity aerobic training may have little or no difference on handgrip strength compared to high- intensity training at 8-week follow-up
		Difference: MD 1.70 lower (CI 95% 1.45 lower - 1.95 lower)			

SarQOL: Sarcopenia and Quality of Life questionnaire; MD: mean difference; CI: confidence interval.

1. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Nambi, 2021].
2. **Imprecision: very serious.** Low number of patients, Only data from one study;
3. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Nambi, 2021].

4. **Imprecision: very serious.** Low number of patients, Only data from one study;
5. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Nambi, 2021].
6. **Imprecision: very serious.** Low number of patients, Only data from one study;
7. Primary study. **Baseline/comparator** Control arm of reference used for intervention. Supporting references [Nambi, 2021].
8. **Imprecision: very serious.** Low number of patients, Only data from one study;

The RCT by Li (2021) compared an unsupervised home-based 6-week exercise program with no exercise. The program comprised breathing control and thoracic expansion, aerobic exercise and limb muscle strength exercise, delivered via smartphone, and remotely monitored with heart rate telemetry. Exercise intensity prescribed for aerobic exercise was based on heart rate reserve and ranged from 30%–40% for tier 1 to 40%–60% for tier 3. The study included 120 patients aged 18–75 years recovering from COVID-19, discharged from 3 hospitals in China. The primary outcome was functional exercise capacity post-treatment measured with the 6 minute walking test (6MWT).

The RCT by Nambi (2021) compared low-intensity aerobic exercise with high-intensity aerobic exercise in community-dwelling older men with post-COVID 19 sarcopenia. All participants performed resistance training with weights based on an individual, personal strength assessment, and were instructed to perform aerobic training exercises for 8 weeks (4 times a week, 30 minutes) by a trained physiotherapist, either at low intensity (40-60% of maximum heart rate) or at high intensity (60-80% of maximum heart rate). The study from Saudi Arabia included 76 men aged 60–80 years with post-COVID-19 sarcopenia, defined as appendicular skeletal muscle mass index score <7.0 kg/m². The primary outcome was handgrip strength.

Zoeken en selecteren

Clinical question

Wat is the value of a physical exercise program in patients at least 4 weeks after SARS-CoV-2 infection. And if this intervention can be endorsed, which frequency, intensity, type and duration of the training should be recommended?

PICO

P: patients at least 4 weeks after SARS-CoV-2 infection

I: structural physical exercise program

C: usual care/no physical exercise program/waiting list control/other (physical) exercise program (yoga, mobilization exercises, personal advise)

O: physical functioning (critical), quality of life (critical), physical fitness (critical), muscle strength (important), fatigue (important), physical activities (important), adverse events (important), return to work (important)

Other selection criteria

Study design: systematic review (SR), randomized controlled trials (RCTs), comparative observational studies.

For the search update (September 2021): SRs and RCTs.

Follow-up: not specified

The databases Medline (via OVID) and Embase (via Embase.com) and Cinahl (via Ebsco) were searched with relevant search terms from inception up to and including June 7, 2021. The search was updated on September 7, 2021. The detailed search strategy is presented under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO (table 1). In the literature searched at Jun 7, eight studies were initially selected based on title and abstract screening. After reading the full text articles, all eight studies were excluded. The appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Physical functioning: as determined with a validated physical performance test (e.g., the 6-minute walk test).
- Quality of Life: as determined with a validated quality of life questionnaire (e.g., 36-item Short Form Health Survey-36, EuroQol-5D). Subscales of quality of life questionnaires were not included.
- Physical fitness: as determined with a cardiopulmonary exercise test (CPET) or submaximal exercise test.
- Muscle strength: as assessed using dynamometry or as expressed as the one repetition maximum or maximal wattage (Wmax).
- Fatigue: as assessed using a validated fatigue questionnaire (e.g. Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS)).
- Physical activity: as determined with accelerometry or pedometry.
- Return to work as defined in the included studies
- Adverse events as defined in the included studies

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference. Given the variety in methods to determine and report adverse events, the working group did not define the minimal clinically (patient) important difference but evaluated the differences after data extraction.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Ademhalingsoefeningen, ademspiertraining en interventies gericht op stemklachten na COVID-19

Uitgangsvraag

Wat is de (toegevoegde) waarde van ademhalingsoefeningen, ademspiertraining en/of interventies gericht op stemklachten (bijvoorbeeld stemoefeningen) bij patiënten ≥ 4 weken na COVID-19?

Aanbeveling

Aanbeveling 1

Voor verwijzers

Overweeg verwijzing naar een logopedist voor ademhalingsoefeningen bij patiënten met doorgemaakte COVID-19 die na 6 weken nog klachten rapporteren, zoals:

- vermoeidheid tijdens het spreken
- gevoel van een samengeknepen keel of globusgevoel

Overweeg verwijzing naar een logopedist, fysio- of oefentherapeut bij patiënten met doorgemaakte COVID-19 die ≥ 6 weken nog klachten rapporteren, zoals:

- disfunctioneel ademhalingspatroon (bijvoorbeeld onregelmatige ademhaling, ademhalingspatroon dat niet past bij de geleverde inspanning, thoracaal adempatroon)
- het niet onder controle krijgen van de ademhaling in rust, tijdens of na lichte inspanningen

Aanbeveling 2

Voor de longarts, sportarts en fysio- of oefentherapeut

Overweeg verwijzing voor ademspiertraining naar een fysio- of oefentherapeut (bevoegd en bekwaam en met beschikking over de benodigde apparatuur) bij patiënten met doorgemaakte COVID-19 die voldoen aan de volgende criteria:

- ademspierzwakte hebben (zie tabel 1)
- geen contra-indicatie hebben
- na de achtste week in het trainingsprogramma nog blijvende dyspneuklachten tijdens inspanning ervaren

De contra-indicaties voor ademspiertraining zijn:

- spontane pneumothorax in voorgeschiedenis
- blessure of een recente operatie ($< 6-8$ weken) waardoor training niet mogelijk is
- astma met regelmatige onverwachte (en zware) exacerbaties
- recent myocardinfarct of andere trombo-embolische aandoeningen
- aneurysma in de boven- of onderbuik

- koorts $\geq 38^{\circ}\text{C}$
- recente of niet-volledige herstelde trommelvliesperforaties en/of KNO-infecties

Voor de fysio- of oefentherapeut die de ademspiertraining geeft

Overweeg bij inzet van ademspiertraining de volgende dosering aan te houden:

- Frequentie: 3 tot 5 dagen in de week, 2 keer per dag 30 ademteugen (eventueel te verdelen in 3 x 10 of 2 x 15 ademteugen)
- Intensiteit: weerstand van 30% van de maximale inademiingsdruk ($P_{i\text{-max}}$) met een ervaren mate van vermoeidheid op de 10-punts Borgschaal van 3 tot 4
- Tijd: 2 x 30 ademteugen per sessie
- Type: Threshold loading device of respiratory training device

Overweeg om de belastbaarheid een keer per 2 weken in gesuperviseerde trainingen te evalueren met behulp van een monddrukmeting.

Aanbeveling 3

Voor verwijzers

Verwijs bij aanhoudende stemklachten, zoals langdurige (≥ 6 weken) heesheid, naar een KNO-arts en eventueel een logopedist. Verwijs bij risicofactoren na ≥ 3 weken stemklachten.

Voor logopedisten en KNO-artsen

Overweeg de richtlijn Stemklachten te volgen bij patiënten met doorgemaakte COVID-19 en stemklachten rapporteren.

Overwegingen

Voor- en nadelen van de interventie

Er zijn geen onderzoeken gevonden die de zoekvraag beantwoorden. Er waren wel 2 onderzoeken die het effect van kortdurende (2 tot 6 weken follow-up) respiratoire revalidatie hebben geëvalueerd bij patiënten na COVID-19 (Liu, 2020; Abondonya, 2021), maar het is onduidelijk of deze interventies ≥ 4 weken na acute infectie zijn gestart. De werkgroep heeft er daarom voor gekozen om deze artikelen niet te includeren. Gezien de beperkingen in de onderzoeksopzet (*risk of bias*) en de beperkte patiëntaantallen (imprecisie) zou inclusie van de artikelen sowieso niet tot een bewijskracht hoger dan 'zeer laag GRADE' voor de gedefinieerde uitkomstmaten hebben geleid.

De werkgroep is op basis van expert opinion van mening dat ademhalingsoefeningen en/of ademspiertraining bij specifieke patiënten overwogen kunnen worden. Bij stemklachten wordt de patiënt normaliter naar een KNO-arts en eventueel logopedist verwezen. De logopedisten en KNO-artsen kunnen de richtlijn Stemklachten (NVKNO, 2016) volgen.

Ademhalingsoefeningen

Een verwijzing naar de logopedist, fysio- of oefentherapeut voor de ademhalingsoefeningen is mogelijk

geïndiceerd bij patiënten na doorgemaakte COVID-19 die na 6 weken nog een disfunctioneel ademhalingspatroon hebben en/of het de ademhaling in rust, tijdens of na lichte inspanning niet onder controle krijgen. Voor de paramedicus is het belangrijk om breed te inventariseren welke (medische, interne en externe) factoren samenhangen met welke klachten en eventueel de interventie hierop aan te passen. Indien er sprake is van aanhoudende (≥ 6 weken) vermoeidheid tijdens spreken en/of een gevoel van een samengeknepen keel, kan een verwijzing naar de logopedist overwogen worden. De werkgroep kiest voor deze periode omdat er binnen de eerste 6 weken na SARS-CoV-2-infectie ook zonder verwijzing herstel kan plaatsvinden.

Ademspiertraining

In tegenstelling tot ademhalingsoefeningen die met minimale weerstand worden uitgevoerd, is ademspiertraining een vorm van krachttraining. Bij conventionele trainingsprotocollen voor ademhalingsspieren is ademen door een apparaat vereist, waarin de weerstand met een klep makkelijk en betrouwbaar in te stellen is. Zodra er voldoende (inspiratoire) druk is gegenereerd, gaat de klep open en stroomt er lucht door het apparaat. Een percentage van de maximale inademiingsdruk (Pi-max) of maximale uitademiingsdruk (Pe-max) wordt gebruikt als trainingsbelasting (intensiteit). Ademspiertraining lijkt positieve effecten te hebben bij verschillende patiëntenpopulaties (zie bijvoorbeeld Chuang, 2017; Gosselink, 2011; Lisboa, 1994; Medeiros, 2019).

Over het algemeen zullen patiënten die baat kunnen hebben bij ademspiertraining al bekend zijn bij een fysio- of oefentherapeut. Bij patiënten met ademspierzwakte (zie tabel 1) die na de achtste week in het trainingsprogramma nog blijvende dyspneuklachten tijdens inspanning houden, kan een indicatie voor ademspiertraining overwogen worden. Voor het bepalen van de ademspierzwakte en de begeleiding van de ademspiertraining is specifieke expertise en apparatuur nodig. Aangezien de expertise voor het bepalen van de spierzwakte voornamelijk ligt bij fysio- of oefentherapeuten, longartsen en sportartsen, ligt het voor de hand dat zij eventuele patiënten verwijzen. Indien de therapeut zich niet bekwaam en/bevoegd acht en/of de apparatuur niet voorhanden is, luidt het advies om de patiënt te verwijzen naar een therapeut die bevoegd en bekwaam is en over de benodigde apparatuur beschikt.

Tabel 1. Drempelwaarde ademspierzwakte*

Leeftijd (in jaren)	Drempelwaarde (in cm H ₂ O)	
	Mannen	Vrouwen
< 40	63	58
40 tot 60	55	50
61 tot 80	47	43
> 80	42	38

*** Waarden overgenomen uit Severin (2020). Deze waarden representeren de maximale inademiingsdruk die geassocieerd wordt met een hogere waarschijnlijkheid dat er sprake is van ademspierzwakte.**

Er zijn een aantal contra-indicaties voor ademspiertraining bekend (Laveneziana, 2019). De werkgroep raadt aan om ook bij patiënten na doorgemaakte COVID-19 rekening te houden met de volgende contra-indicaties voor ademspiertraining:

- spontane pneumothorax in voorgeschiedenis
- blessure of een recente operatie (< 6-8 weken) waardoor training niet mogelijk is
- astma met regelmatige onverwachte (en zware) exacerbaties
- recent myocardiinfarct of andere trombo-embolische aandoeningen
- aneurysma in de boven- of onderbuik
- koorts $\geq 38^{\circ}\text{C}$
- recente of niet-volledige herstelde trommelvliesperforaties en/of KNO-infecties

Bij de dosering van de ademspiertraining lijkt het belangrijk om zowel duurtraining (flow genererend, hoge snelheid, lage weerstand) als krachttraining (druk genererend, hoge weerstand, lage snelheid) op te nemen in het programma. Na een instructie kan de patiënt veelal zelf met de training aan de slag. Uiteraard moet de belastbaarheid van de patiënt in ogenschouw worden gehouden. Het wordt aangeraden om de belastbaarheid een keer per 2 weken in gesuperviseerde trainingen te evalueren met behulp van een monddrukmeter. Overweeg als startpunt van de trainingen de volgende dosering:

- Frequentie: 3 tot 5 dagen in de week, 2 keer per dag 30 ademteugen (eventueel te verdelen in 3x10 of 2x15 ademteugen)
- Intensiteit: weerstand van 30% van de maximale inademiingsdruk ($P_{i\text{-max}}$) met een ervaren mate van vermoeidheid op de 10-punts Borgschaal van 3 tot 4
- Tijd: 2 keer per dag 30 ademteugen
- Type: threshold loading device of respiratory training device

Kwaliteit van bewijs

Er zijn geen onderzoeken gevonden. De kwaliteit van het bewijs is dus zeer laag.

Waarden en voorkeuren van patiënten

Voor patiënten is het belangrijk om de ademhaling onder controle te hebben en geen benauwdheid te ervaren. De verwachting is dat de meeste patiënten positief staan tegenover de inzet van deze ademhalingsoefeningen en ademspiertraining. Sommige patiënten ervaren ademhalingsoefeningen ook als ontspannend en bijdragend aan de kwaliteit van slaap en/of rustmomenten door de dag heen.

Kosten

Er is geen informatie beschikbaar over de kosteneffectiviteit van de ademhalingsoefeningen of ademspiertraining. Bij inzet van 1 van de interventies worden er kosten gemaakt voor de gesuperviseerde behandelingen door een paramedicus, het bepalen of er sprake is van spierzwakte en het gebruik van apparatuur (in het geval van ademspiertraining). Voor het vaststellen/meten van ademspierzwakte moet zowel de in- als expiratoire monddruk worden gemeten. Er zijn verschillende trainingsapparaten voor het trainen van de in- en expiratoire ademspieren op de markt, waarbij de prijs varieert tussen de € 30 en € 300. De goedkopere opties voldoen in principe. Deze trainingsapparaten zijn niet voor meerdere patiënten te gebruiken.

De kosten van de gesuperviseerde behandeling worden vergoed vanuit de regeling Paramedische

herstelzorg indien de verwijzing < 6 maanden na afloop van het acute infectiestadium wordt gegeven. Buiten de herstelzorgregeling kan de patiënt een beroep doen op de basis- of de aanvullende verzekering. De regeling loopt vooralsnog tot augustus 2022. De patiënt dient de trainingsapparatuur zelf aan te schaffen.

Aanvaardbaarheid, haalbaarheid en implementatie

Naar verwachting is er in Nederland voldoende kennis en kunde beschikbaar. Niet alle oefen- en fysiotherapiepraktijken hebben de beschikking over de apparatuur om ademspierkrachttraining te bepalen, maar naar verwachting zijn er voldoende fysiotherapeuten in Nederland die hier wel over beschikken. Elke patiënt krijgt in principe zijn eigen mondstuk; er zijn geen zorgen over de verspreiding van COVID-19 bij het gebruik van de apparatuur.

Ten aanzien van aanvaardbaarheid, haalbaarheid en implementatie zijn er verder geen overwegingen die van invloed zijn op de besluitvorming.

Rationale van de aanbevelingen

Aanbeveling 1

Ondanks het gebrek aan wetenschappelijke onderbouwing, verwacht de werkgroep dat ademhalingsoefeningen een positief effect kunnen hebben bij patiënten die ≥ 6 weken nog klachten rapporteren als vermoeidheid tijdens het spreken, een disfunctioneel ademhalingspatroon, het gevoel van een samengeknepen keel of globusgevoel en/of het niet onder controle krijgen van de ademhaling in rust, tijdens of na lichte inspanning. De werkgroep kiest daarom voor een zwak positieve aanbeveling over de inzet van ademhalingsoefeningen bij deze patiënten.

Aanbeveling 2

Ondanks het gebrek aan wetenschappelijke onderbouwing, verwacht de werkgroep dat ademspiertraining een positief effect kan hebben bij patiënten die > 8 weken in het fysieke trainingsprogramma nog blijvende dyspneuklachten tijdens inspanning ervaren en ademspierzwakte hebben. De werkgroep raadt daarom aan om bij deze patiënten een verwijzing naar een fysio- of oefentherapeut (bevoegd en bekwaam en met beschikking over de benodigde apparatuur) te overwegen.

Aanbeveling 3

Patiënten met stemproblemen, zoals langdurige (≥ 6 weken) heesheid, worden normaliter doorgestuurd naar de KNO-arts. Bij risicofactoren is een eerdere verwijzing op zijn plaats. Bij patiënten die COVID-19 hebben doorgemaakt kan eventueel ook een gelijktijdige verwijzing naar de logopedist worden overwogen. Voor de logopedist en KNO-arts is de richtlijn Stemklachten beschikbaar. Overwogen kan worden om deze richtlijn ook bij patiënten met doorgemaakte COVID-19 te volgen.

Onderbouwing

Achtergrond

Dyspneu is een veelvoorkomende klacht na COVID-19 (NICE, 2020). Kortademigheidsklachten kunnen voorkomen als er bijvoorbeeld sprake is van een snel en oppervlakkig adempatroon of als er onvoldoende kracht en uithoudingsvermogen van de ademhalingspierspiers is. Ademhalingsoefeningen of ademspiertraining

zorgen mogelijk voor een afname van kortademigheid en toename van de inspanningstolerantie. Dergelijke oefeningen kunnen patiënten helpen om de fysieke inspanningen beter te tolereren en sneller vooruitgang te boeken. Een disfunctionele ademhaling[1] (bijvoorbeeld een onregelmatige ademhaling, een ademhalingspatroon dat niet past bij de geleverde inspanning of een thoracaal adempatroon) kan ook gepaard gaan met stemproblemen, waarvoor adem- en stemoefeningen geïndiceerd kunnen zijn.

[1] Paraplueterm, hier gedefinieerd als ademhalingsproblemen waarbij chronische veranderingen in het ademhalingspatroon resulteren in dyspneu en andere symptomen, en niet veroorzaakt worden door andere aanwezige ziekten (Boulding, 2016).

Samenvatting literatuur

It was not possible to provide a summary of literature, because none of the studies fulfilled the PICO-criteria.

Zoeken en selecteren

Clinical question

What are the beneficial and unfavourable effects of breathing exercises, respiratory rehabilitation, and/or interventions targeting voice complaints (e.g. voice exercises) in adult patients ≥ 4 weeks from onset of COVID-19?

PICO

P: Adult patients who have experienced COVID-19 (≥ 4 weeks from onset of COVID-19 illness)

I: A. respiratory muscle training; B. breathing exercises; C. respiratory rehabilitation; D. interventions targeting voice complaints, e.g. voice exercises

C: Placebo, usual care, other types of interventions (e.g. yoga, relaxation, functional training)

O: dyspnea (critical), physical functioning (critical), quality of life (important), respiratory muscle strength (important), participation (important), severity and consequences of voice complaints (important)

Other selection criteria

A minimum of 10 patients per study arm.

Study design: systematic review, RCTs, comparative observational studies.

Follow-up: not specified.

The databases Medline (via OVID), Embase (via Embase.com), and Cinahl (via Ebsco.com) were searched with relevant search terms until June 14th, 2021. The search was updated on September 7th, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the criteria as described the PICO. The appendices (*Bijlagen*) contain the PRISMA flowcharts of the first search and the update, showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Dyspnea: as determined using a validated instrument, assessed at rest, during exercise, and/or during speech.

- Physical functioning: as determined with a validated physical performance test or validated questionnaires.
- Quality of Life: as determined with a validated quality of life questionnaire (for example 36-item Short Form Health Survey, EuroQol-5D).
- Respiratory muscle strength: as expressed as the Pi-max and/or Pe-max.
- Participation: as determined with a validated participation questionnaire.
- Severity and consequences of voice complaints: as determined with the voice handicap index

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

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Energiemanagement na COVID-19

Uitgangsvraag

Wat is de waarde van het inzetten van begeleiding met betrekking tot energiemangement bij patiënten met aanhoudende vermoeidheidsklachten ≥ 4 weken na COVID-19?

Aanbeveling

Voor verwijzers

Overweeg patiënten die vermoeidheidsklachten houden (≥ 6 weken) en daardoor ernstige problemen ervaren in de uitvoer van dagelijkse activiteiten en/of werkhervatting, te verwijzen naar een gespecialiseerde zorgprofessional, zoals de ergotherapeut, voor begeleiding met betrekking tot energiemangement.

Overwegingen

Voor- en nadelen van de interventie

Er zijn geen onderzoeken gevonden. Het is onbekend of begeleiding met betrekking tot energiemangement bij patiënten met aanhoudende vermoeidheid na het doormaken van een SARS-CoV-2-infectie effectief is met betrekking tot vermoeidheid, kwaliteit van leven, terugkeer naar werk, algemene dagelijkse levensverrichtingen (ADL), fysieke activiteitsniveau en adverse events. Hier ligt duidelijk een kennislacune.

Toch is de werkgroep van mening dat begeleiding bij energiemangement een waardevolle interventie kan zijn voor patiënten die (≥ 6 weken) vermoeidheidsklachten blijven ervaren na het doormaken van COVID-19. Op basis van praktijkervaring is de ervaring van de werkgroep dat begeleiding met betrekking tot energiemangement door een ergotherapeut bij patiënten die ernstige vermoeidheidsklachten ervaren en daardoor beperkingen in de uitvoer van dagelijkse activiteiten en/of werkhervatting, zeer nuttig is. Er is gekozen voor ≥ 6 weken, aangezien er in de eerste periode, eventueel met behulp van adviezen door de arts (zie de module Natuurlijk beloop), ook zonder begeleiding van de ergotherapeut herstel kan optreden.

Ergotherapeuten en (psychosomatisch) fysio- of oefentherapeuten werken veelal samen bij energiemangement: een goede energiebalans en een goede opbouw van de eigen mogelijkheden wordt immers bereikt als zowel de uitvoer van dagelijkse activiteiten en/of werkhervatting alsmede een fysieke (oefen)programma goed op elkaar zijn afgestemd. Het uitgangspunt is dat daarmee ook de eigen regie van de patiënt in zijn herstelproces wordt aangesproken en versterkt.

Zie voor meer informatie over ergotherapie en over de begeleiding met betrekking tot energiemangement de bijlage Toelichting Ergotherapie en Energiemangement bij deze module.

Kwaliteit van bewijs

Er zijn geen onderzoeken gevonden. De kwaliteit van het bewijs is dus zeer laag.

Waarden en voorkeuren van patiënten

De patiënten hebben voornamelijk als doel om de ADL en hun werkzaamheden beter uit te kunnen voeren, de pieken en dalen te verminderen en minder vermoeidheidsklachten te ervaren. Veel patiënten zijn

enthousiast over de inzet van de ergotherapeut en raden deze begeleiding ook aan bij lotgenoten. Patiënten geven voornamelijk aan dat ze meer structuur krijgen en controle ervaren.

Kosten

Anno 2021 is ergotherapie opgenomen in het basispakket (10 uur per patiënt per kalenderjaar). In de huidige regeling Paramedische herstellzorg na COVID-19 is 10 uur per halfjaar beschikbaar. Deze regeling loopt vooralsnog tot 1 augustus 2022. In principe is de vergoeding toereikend. De kosten zijn niet van dien aard dat ze van invloed zijn op de besluitvorming.

Aanvaardbaarheid

Er worden geen aanvaardbaarheidsproblemen verwacht.

Haalbaarheid

Ergotherapeuten kunnen specifieke nascholing volgen op het gebied van energiemangement. De werkgroep is van mening dat het wenselijk is dat de patiënt begeleid wordt door een ergotherapeut die bekwaam is in het geven van begeleiding bij energiemangement. De verwachting is dat er in de meeste regio's in Nederland voldoende kennis en kunde op dit vlak aanwezig is. De eventuele inzet van groepsbehandelingen zou de haalbaarheid positief kunnen beïnvloeden.

Waarom deze aanbeveling/rationale?

Er is geen wetenschappelijk bewijs beschikbaar. De werkgroep kiest echter op basis van expert opinion en het patiëntenperspectief voor een zwak positieve aanbeveling met betrekking tot energiemangement.

Onderbouwing

Achtergrond

Na het doormaken van COVID-19 blijven veel mensen lang moe. Een van de behandelmogelijkheden is interveniëren in het kader van energiemangement. Met energiemangement wordt bedoeld dat iemand leert de beschikbare energie te verdelen over de dag, keuzes te maken en prioriteiten te stellen in dagelijkse activiteiten passend bij de maximale fysieke en mentale belastbaarheid. Om een gezonde energiebalans te creëren in de dagelijkse activiteiten zijn momenten van rust en ontspanning essentieel. Op dit moment is nog onvoldoende bekend wat het effect is van begeleiding met betrekking tot energiemangement op de vermoeidheid na COVID-19.

Samenvatting literatuur

It was not possible to provide a summary of literature, because none of the studies fulfilled the PICO-criteria.

Zoeken en selecteren

Clinical question

What is the value of the teaching patients with persisting fatigue ≥ 4 weeks post SARS-CoV-2 infection energy management strategies?

PICO

P: Patients who are ≥ 4 weeks post SARS-CoV-2 infection and experience persisting fatigue

I: Energy management, occupational therapy

C: Usual care, which could for instance include physiotherapy / attention control/ waitlist control

O: Fatigue (critical), quality of life (critical), return to work (important), ADL (important), physical activity (important), adverse events (important; incl. post-exertional malaise; PEM)

Other selection criteria

Study design: systematic review, randomized controlled trials and comparative observational studies.

for the search update (September 2021): randomized controlled trials and systematic reviews of randomized controlled trials.

The databases Medline (via OVID), Embase (via Embase.com) and Cinahl (via Ebsco.com) were searched with relevant search terms from January, 1st 2019 until April 28th. The search was updated on September 5th, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the criteria as described in the PICO. The appendices (*Bijlagen*) contain the PRISMA flowchart showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows.

- Fatigue: as assessed using a validated fatigue questionnaire (e.g. Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS)).
- Quality of Life: as determined with a validated quality of life questionnaire (e.g., 36-item Short Form Health Survey-36 (SF-36), EuroQol-5D).
- Physical activity: as determined with accelerometry or pedometry.

The working group did not predefine the outcome measures return to work, activities of daily living and return to work, but used the definitions used in the included studies.

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference. Given the huge variety in methods to determine and report adverse events, the working group did not a priori define the minimal clinically (patient) important difference for this outcome measure. The differences between the groups were evaluated by the working group after data extraction.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Behandeling van cognitieve klachten na COVID-19

Uitgangsvraag

Wat is de waarde van cognitieve revalidatie, psycho-educatie en/of cognitieve gedragstherapie bij patiënten met cognitieve klachten ≥ 4 weken na COVID-19, zonder aantoonbaar of aannemelijk hersenletsel?

Aanbeveling

Bespreek dat:

- de klachten naar verwachting tijdelijk zijn
- het belangrijk is om in- en ontspanning af te wisselen en om activiteiten geleidelijk op te bouwen (zie ook de modules Energiemanagement en Fysiek trainingsprogramma).

Overweeg een verwijzing naar een ergotherapeut bij patiënten met aanhoudende (≥ 3 maanden) cognitieve klachten, die problemen geven in het dagelijks functioneren.

Overweeg, indien psychosociale factoren (zoals copingstijl) de opbouw in de weg staan, begeleiding door de POH-ggz of maatschappelijk werker/sociaal werker of verwijzing naar een eerstelijns psycholoog.

Overweeg, als het herstel ondanks begeleiding door een ergotherapeut (≥ 3 maanden) uitblijft of bij het vermoeden van ernstigere cognitieve problematiek, een verwijzing naar de specialistische zorg (revalidatiearts, neuropsycholoog of neuroloog).

Overwegingen

Voor- en nadelen van de interventie

Er zijn geen onderzoeken gevonden die de zoekvraag beantwoorden. Het is dus onbekend of de interventies bij patiënten die COVID-19 hebben doorgemaakt en ≥ 4 weken na infectie aanhoudende cognitieve klachten hebben, effectief zijn met betrekking tot subjectieve cognitieve klachten, cognitief functioneren, kwaliteit van leven, terugkeer naar werk, angst en depressie. Hier ligt duidelijk een kennislacune.

De werkgroep adviseert enkel cognitieve revalidatie voor patiënten met hersenletsel. Aanvullende diagnostiek (zie de module MRI-hersenen) wordt alleen geadviseerd als COVID-19 heeft geleid tot aantoonbaar of aannemelijk hersenletsel door complicaties, zoals een hersenbloeding, herseninfarct of ernstig zuurstoftekort. Bij patiënten die niet ernstig ziek zijn geweest door COVID-19 en bij wie er geen sprake is van een afwijkend beloop, ligt de aanwezigheid van hersenletsel niet voor de hand. De cognitieve klachten die deze groep ervaart moeten wel degelijk serieus genomen worden, gezien de mogelijk negatieve invloed op onder andere het dagelijkse handelen, emotioneel functioneren, kwaliteit van leven, terugkeer naar werk, belastbaarheid en relaties.

De werkgroep is van mening dat het biopsychosociale model passend is bij het verklaren en aanpakken van de cognitieve klachten na COVID-19, omdat cognitief functioneren wordt beïnvloed door meerdere factoren (sociaal, psychologisch, fysiek).

De werkgroep adviseert het 'stepped care'-principe te volgen bij cognitieve klachten na COVID-19:

1. Start met het erkennen van de cognitieve klachten en geef goede uitleg en tips. Erken en normaliseer cognitieve klachten na COVID-19: goede educatie kan eventuele onzekerheden bij patiënten wegnemen. Benadruk dat goed en spontaan herstel te verwachten is enkele maanden na COVID-19. Leg uit dat cognitieve klachten een logisch gevolg zijn van het feit dat het lijf bij het herstellen meer energie verbruikt. Hierdoor is er minder energie over voor het brein, leidend tot mentale vermoeidheid en cognitieve klachten. Naast de fysieke impact kan ook de emotionele impact van COVID-19 een negatief effect hebben op het cognitieve functioneren, omdat de emotionele aanpassing energie kost. Leg hiernaast eventueel uit dat er een langer durende disbalans kan zijn tussen het sympathische zenuwstelsel (stresssysteem) en het parasympatische zenuwstelsel (ontspanningssysteem), met cognitieve klachten tot gevolg. Het is daarom belangrijk om in- en ontspanning af te wisselen en rustig op te bouwen (zie ook de modules Energiemanagement en Fysiek trainingsprogramma). Als de patiënt meer balans ervaart en energie heeft, nemen de cognitieve klachten naar verwachting spontaan af. Wijs patiënten ook op de informatie op Thuisarts.nl en geef eventueel de zelfhulptips van Ergotherapie Nederland. Deze tips zijn waarschijnlijk behulpzaam bij cognitieve klachten en herstel van COVID-19.
2. Overweeg een verwijzing naar een ergotherapeut bij patiënten met aanhoudende cognitieve klachten $\geq$ 3 maanden, die problemen geven in het dagelijks functioneren. We kiezen voor een termijn van 3 maanden, omdat de verwachting is dat een gedeelte van de klachten spontaan herstelt. De ergotherapeut kan interventies inzetten die aansluiten op de mogelijkheden van de patiënt. De interventies bestaan bijvoorbeeld uit:
 - begeleiding met betrekking tot energimanagement (zie de module Energiemanagement); hiermee wordt bedoeld dat de patiënt leert om de beschikbare energie goed over de dag te verdelen, keuzes te maken en prioriteiten te stellen in dagelijkse activiteiten, passend bij de maximale fysieke en mentale belastbaarheid. Het beoogt een geleidelijke opbouw in activiteiten.
 - cognitieve compensatiestrategieën: hiermee wordt het (tijdelijk) toepassen van strategieën bedoeld, die de patiënt kan inzetten om de cognitieve klacht te compenseren. Dit kunnen interne strategieën zijn (zoals het inzetten van bewuste aandacht en verbale ondersteuning voor het onthouden van informatie) en externe strategieën (zoals het gebruik maken van een herinnering in de telefoon).
3. Als er aanwijzingen zijn voor psychosociale factoren die een negatieve invloed hebben op het cognitieve functioneren of de opbouw van activiteiten in de weg staan (zoals emotionele problemen, persoonlijkheidsfactoren, inadequate copingstijl, gestoord dag-nachtritme), overweeg dan begeleiding door de POH-ggz maatschappelijk werk/sociaal werk of een verwijzing naar de generalistische basis-ggz (BGGZ).
4. Overweeg, als het herstel van de cognitieve klachten ondanks adequate eerstelijnsbehandeling uitblijft of bij het vermoeden van ernstigere cognitieve problematiek, verwijzing naar de specialistische zorg (bijvoorbeeld revalidatiearts, neuropsycholoog of neuroloog).

Bij patiënten met vraag naar aanvullende diagnostiek volstaat over het algemeen psycho-educatie en uitleg over de zeer beperkte waarde van aanvullende diagnostiek (zie de module MRI-hersenen). Mocht dit niet voldoen, overweeg dan volgens het 'stepped care'-model de inzet van een psycholoog, revalidatiearts of

neuroloog.

Kwaliteit van bewijs

Er zijn geen onderzoeken gevonden. De kwaliteit van het bewijs is dus zeer laag.

Waarden en voorkeuren van patiënten

Het belangrijkste doel voor de patiënt is om goed te kunnen participeren. Hiervoor is het van belang dat de cognitieve klachten verminderen. Patiënten hechten verder aan (h)erkenning van de klachten en vinden het belangrijk om betrouwbare informatie te ontvangen. Sommige patiënten zullen behoefte hebben aan aanvullende diagnostiek.

In het geval van een verwijzing in verband met de cognitieve klachten hebben sommige patiënten een voorkeur voor een specifiek type zorgverlener (bijvoorbeeld POH-ggz, ergotherapeut, revalidatiearts of (neuro)psycholoog). Het is belangrijk om de verschillende opties met de patiënt te bespreken.

Kosten

Er zijn geen gegevens over de kosteneffectiviteit van de mogelijke verwijzingen en interventies bekend. De werkgroep adviseert behandeling volgens het 'stepped care'-principe. Daarbij zijn de kosten veelal gedekt door de basis- of aanvullende verzekering.

Aanvaardbaarheid

Behandeling volgens het 'stepped care'-principe is in Nederland mogelijk en geaccepteerd.

Haalbaarheid

Er worden geen haalbaarheidsproblemen verwacht. Er is in Nederland voldoende kennis en kunde beschikbaar.

Waarom deze aanbeveling/rationale?

Er zijn geen vergelijkende onderzoeken gevonden die de zoekvraag beantwoorden. De werkgroep doet een sterke aanbeveling om bij cognitieve klachten te starten met het erkennen en uitleg geven over de mogelijke etiologie en samenhangende factoren. De werkgroep doet een zwakke aanbeveling voor verwijzing voor diverse interventies, gezien de schaarsheid van wetenschappelijke literatuur. We kiezen voor een termijn van 3 maanden voor deze interventies, omdat in de eerste periode na de infectie vaak nog spontaan herstel optreedt.

Onderbouwing

Achtergrond

Cognitieve klachten behoren tot de meest frequente langetermijnklachten na COVID-19 (Almeria, 2020; Miskowiak, 2021; NICE, 2020). Patiënten die COVID-19 hebben doorgemaakt kunnen cognitieve klachten ervaren, zoals vergeetachtigheid, concentratie- en aandachtsproblemen en overprikkelingsverschijnselen. In deze module wordt onderzocht of de inzet van cognitieve revalidatie, psycho-educatie en/of cognitieve

gedragstherapie meerwaarde heeft bij patiënten met cognitieve klachten zonder aantoonbaar of aannemelijk hersenletsel. Voor patiënten met hersenletsel na COVID-19 wordt verwezen naar de richtlijn [Herseninfarct en hersenbloeding](#) (NVN, 2017, laatst beoordeeld 2019).

Samenvatting literatuur

It was not possible to provide a summary of literature, because none of the studies fulfilled the PICO-criteria.

Zoeken en selecteren

Clinical question

What is the value of cognitive rehabilitation, psycho-education and/or cognitive behavioural therapy in patients at least 4 weeks after COVID-19 with cognitive complaints, without brain injury?

PICO

P: Patients at least 4 weeks after COVID-19 with cognitive complaints, without brain injury

I: Cognitive rehabilitation, psycho-education, cognitive behavioural therapy

C: No intervention, waiting list control

O: (Subjective) cognitive complaints (crucial), cognitive functioning (crucial), quality of life (important), return to work (important), anxiety (important), depression (important)

Other selection criteria

Study design: systematic review or meta-analysis, RCT, other comparative research.

For the search update (September 2011): randomized controlled trials and systematic reviews of randomized controlled trials.

The databases Medline (via OVID), Embase (via Embase.com) and Psycinfo were searched with relevant search terms from 2019 until May 18th, 2021. The search was updated on September 5th, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the following criteria as described in the PICO. The appendices (*Bijlagen*) contain the [PRISMA flowchart](#) showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows:

- (Subjective) cognitive complaints, as assessed by a trained health care professional or determined using a validated questionnaire.
- Cognitive functioning, as determined using a validated test/screening instrument or questionnaire.
- Quality of life: as determined with a validated quality of life questionnaire (e.g., 36-item Short Form Health Survey-36 (SF-36), EuroQol-5D).
- Anxiety: as determined using a validated questionnaire (e.g., the Hospital Anxiety and Depression Scale – Anxiety subscale (HADS-A))
- Depression: as determined using a validated questionnaire (e.g., the Hospital Anxiety and Depression Scale – Depression subscale (HADS-D))

The working group did not predefine the important outcome return to work, but used the definitions used in the included studies.

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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Psychologische interventies na COVID-19

Uitgangsvraag

Wat is de waarde van een psychologische behandeling bij patiënten ≥ 4 weken na COVID-19 met aanhoudende psychische en/of lichamelijke klachten?

Aanbeveling

Geef erkenning voor de klachten van de patiënt. Start met voorlichting, adviezen en/of psycho-educatie aan de patiënt.

Overweeg tijdens de eerste maanden van het herstel *watchful waiting* bij milde angst en/of somberheid toe te passen. Verwijs in deze fase wel bij ernstige klachten en/of een copingstijl die het herstel belemmeren.

Behandel na drie maanden psychische klachten (klachten die passen bij PTSS, een angst- of depressieve stoornis) alsmede aanhoudende lichamelijke klachten waarbij er een probleem is in de copingstijl volgens de geldende richtlijnen. Hierbij hebben voorlichting en gedragsinterventies een belangrijke plek.

Volg bij slapeloosheid de geldende richtlijnen.

Overwegingen

Voor- en nadelen van de interventie

Er is slechts 1 onderzoek gevonden. In dit onderzoek werd onderzocht of een specifieke vorm van cognitieve gedragstherapie plus een persoonlijke psychologische interventie effectiever was ten opzichte van een persoonlijke psychologische interventie bij patiënten met klachten passend bij PTSS. Er werden alleen groepseffecten gevonden voor de klachten passend bij PTSS. Het is hiermee echter nog grotendeels onbekend of psychologische behandelingen ten opzichte van geen behandeling bij patiënten die COVID-19 hebben doorgemaakt en ≥ 4 weken na infectie aanhoudende psychische en/of lichamelijke klachten hebben effectief is met betrekking tot vermoeidheid, subjectieve cognitieve klachten, angst, depressie, kwaliteit van leven, terugkeer naar werk, slaap en adverse events.

Veelvoorkomende klachten die gezien worden na COVID-19 zijn herbeleving, angst (ook voor herbesmetting), slaapklachten en aanhoudende lichamelijke klachten waarvoor (nog) geen somatische interventies beschikbaar zijn, zoals vermoeidheid en pijn. Deze klachten zijn waarschijnlijk niet specifiek voor COVID-19. Het is belangrijk dat alle zorgprofessionals deze klachten bespreekbaar maken. Ook is het belangrijk dat zorgprofessionals diagnostiek en behandeling inzetten volgens het biopsychosociale model en dat klachten worden erkend, ook als er geen lichamelijke oorzaak vastgesteld kan worden. De eerste onderzoeksresultaten laten zien dat een groot deel van de klachten in de loop van de tijd verdwijnen. Het is belangrijk om dit ook aan de patiënt mee te geven. Voorlichting, adviezen en/of psycho-educatie zijn vaak al behulpzaam.

Gezien de grote kans op natuurlijk herstel wordt aangeraden om in de initiële herstelfase (< 3 maanden) *watchful waiting* bij angst en/of somberheid toe te passen. *Watchful waiting* impliceert terughoudend zijn met behandeling, maar alert te zijn op potentiële problemen en indien nodig proactief te handelen. Indien

psychische klachten het (functioneel) herstel in de weg staan, dient hiervoor wel professionele ondersteuning te worden aangeboden.

Als de klachten persisteren (≥ 3 maanden), kan een interventie ingezet worden. Voor angst, depressie en trauma zou gebruik gemaakt kunnen worden van de betreffende richtlijnen. Voor de lichamelijke klachten is een benadering vanuit het biopsychosociale model belangrijk. Voorbeelden van een richtlijn die hiervoor gevolgd kunnen worden is het Q-koorts vermoeidheidssyndroom (RIVM, 2019) en richtlijnen voor aanhoudende lichamelijke klachten (ALK)/SOLK (Olde Hartman, 2013). Over het algemeen hebben voorlichting, psycho-educatie en gedragsinterventies hierbij een belangrijke plek. Onder deze interventies vallen ACT, mindfulness en CGT.

Ook bij chronische slapeloosheid (insomnie) kunnen de beschikbare richtlijnen worden gevolgd. Hierbij ligt de nadruk op gedragsinterventies, die bijvoorbeeld gericht zijn op verbetering van de slaaphygiëne en het normaliseren van het slaap-waakritme.

Kwaliteit van bewijs

De kwaliteit van het bewijs is zeer laag vanwege het feit dat er maar 1 onderzoek is gevonden en niet alle cruciale uitkomstmaten zijn opgenomen.

Waarden en voorkeuren van patiënten

Voor patiënten is het belangrijk dat de klachten serieus genomen worden en dat de mogelijke oorzaken onderzocht zijn. Het is belangrijk dat de zorgprofessional ruimte biedt voor samen beslissen en de adviezen ook specifiek op de patiënt afstemt.

Over het algemeen zal een groot gedeelte van de patiënten na een overleg met de arts en eventueel zijn/haar omgeving positief staan tegenover een psychologische behandeling.

Kosten

De interventies voor angst, depressie en ALK/SOLK worden vergoed vanuit de basisverzekering. De kosten hebben geen invloed op de besluitvorming.

Aanvaardbaarheid

Gezien de grote aantallen patiënten, lijkt het belangrijk na te gaan welke patiënten ook in de eerste lijn (door een psycholoog werkzaam in de generalistische basis-ggz of POH-ggz) geholpen kunnen worden.

Haalbaarheid

De capaciteit om patiënten met aanhoudende klachten te begeleiden, is beperkt. Dit is een mogelijk knelpunt. Over het algemeen zijn er voldoende POH's-ggz beschikbaar, maar de wachttijd bij de psychologen is aanzienlijk opgelopen.

Waarom deze aanbeveling/rationale?

Het is belangrijk dat de klachten van de patiënt erkend worden en dat de diagnostiek en behandeling volgens het biopsychosociale model plaatsvindt. Er kan gestart worden met voorlichting, adviezen en/of psycho-educatie. De werkgroep doet hiervoor een sterke aanbeveling. Met betrekking tot *watchfull waiting* kiest de

werkgroep voor een zwakke aanbeveling, gezien de beperkte wetenschappelijke literatuur. De werkgroep doet daarnaast sterke aanbevelingen om patiënten wel te verwijzen bij ernstige klachten en/of een copingstijl die het herstel belemmeren, patiënten ≥ 3 maanden volgens de geldende behandelrichtlijnen te behandelen en de geldende richtlijnen te volgen bij chronische slapeloosheid.

Onderbouwing

Achtergrond

Een deel van de patiënten na doorgemaakte COVID-19 heeft aanhoudende psychische en lichamelijke klachten. Momenteel zijn er alleen richtlijnen voor andere patiëntgroepen die wat betreft klachten deels overlappen met patiënten met aanhoudende klachten na COVID-19, zoals patiënten met Myalgische Encefalomyelitis (ME/CVS), Aanhoudende lichamelijke klachten (ALK)/Somatisch onvoldoende verklaarde lichamelijke klachten (SOLK) en Q-koorts vermoeidheidssyndroom.

Conclusies / Summary of Findings

Cognitive behavioral therapy plus personalized psychological intervention may improve PTSD more than a personalized psychological intervention.

Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on anxiety when compared to a personalized psychological intervention.

Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on depression when compared to a personalized psychological intervention.

Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on sleep when compared to a personalized psychological intervention.

Because of the absence of relevant comparative studies, no conclusions could be drawn with regard to

- other types of interventions; and
- the effectiveness of cognitive behavioral therapy plus personalized psychological intervention when compared to a personalized psychological intervention on the outcome measures fatigue, subjective cognitive complaints, quality of life, return to work and adverse events.

Samenvatting literatuur

One study was included in the analysis of the literature (Table 1).

Table 1. Summary of Evidence

Population: Patients at least 4 weeks after COVID-19 infection with persistent psychological and / or physical complaints (with no transient medical cause)

Intervention: CBT, ACT, IPT, EMDR, psychological intervention, psycho-education

Comparator: Usual care, waiting list control, no intervention

Outcome	Study results and measurements	Absolute effect estimates		Certainty of the Evidence (Quality of evidence)	Plain language summary
		Control	Psychological intervention		

PTSD	Measured by: PCL-C Scale: 17 - 85 Lower better Based on data from 111 patients in 1 studies Follow up post- intervention	58.65 Mean	9.52 Mean	Low Due to serious risk of bias, Due to serious imprecision ¹	Cognitive behavioral therapy plus personalized psychological intervention may improve PTSD more than a personalized psychological intervention
		Difference: MD 9.13 lower (CI 95% 11.89 lower - 6.37 lower)			
Anxiety	Measured by: SAS Scale: 20 - 80 Lower better Based on data from 111 patients in 1 studies Follow up post- intervention	50.7 Mean	51.64 Mean	Low Due to serious risk of bias, Due to serious imprecision ²	Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on anxiety when compared to a personalized psychological intervention
		Difference: MD 0.84 higher (CI 95% 2.73 lower - 4.61 higher)			
Depression	Measured by: SDS Scale: - Lower better Based on data from 111 patients in 1 studies Follow up post- intervention	50.4 Mean	46.89 Mean	Low Due to serious risk of bias, Due to serious imprecision ³	Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on depression when compared to a personalized psychological intervention
		Difference: MD 3.51 lower (CI 95% 6.84 lower - 0.18 lower)			

Sleep	Measured by: PQSI Scale: 0 - 21 Lower better Based on data from 111 patients in 1 studies Follow up post- intervention	14.31 Mean	13.16 Mean	Low Due to serious risk of bias, Due to serious imprecision ⁴	Cognitive behavioral therapy plus personalized psychological intervention may have little or no difference on sleep when compared to a personalized psychological intervention
		Difference: MD 1.15 lower (CI 95% 2.22 lower - 0.08 lower)			

1. **Risk of Bias: serious.** Selective outcome reporting, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias; **Imprecision: serious.** Only data from one study, Low number of patients;
2. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: serious.** Low number of patients, Only data from one study;
3. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: serious.** Only data from one study, Low number of patients;
4. **Risk of Bias: serious.** Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias, Selective outcome reporting; **Imprecision: serious.** Only data from one study, Low number of patients;

Abbreviations: PCL-C=PTSD Checklist-Civilian Version; SAS=Self-rating Anxiety Scale; SDS=Self-rating Depression Scale; PSQI=the Pittsburgh Sleep Quality Index.

Description of studies

Fan (2021) performed a randomized controlled trial and evaluated the effect of Narrative Exposure Therapy (NET) on discharged COVID-19 patient with positive screening results for posttraumatic stress symptoms (PTSS). In total, 111 patients (mean age: 46 years; 38% male; mean duration of isolation: 40 days) were randomized (1:1) into two groups. The intervention group (n=56) received eight weeks of NET, a typical cognitive behavioral therapy targeting trauma-related psychological disorders in combination with personalized psychological intervention. The control group (n=55) received personalized psychological intervention. The effects were evaluated on participants' post-traumatic stress symptoms, assessed with the PTSD Checklist-Civilian Version (PCL-C); anxiety, assessed with the Self-rating Anxiety Scale (SAS) and depression level, assessed with the Self-rating Depression Scale (SDS).

Zoeken en selecteren

Clinical question

What are the (un) favourable effects of psychological treatment in patients at least 4 weeks after COVID-19 with persistent psychological and / or physical symptoms?

PICO

P: Patients at least 4 weeks after COVID-19 infection with persistent psychological and / or physical symptoms.

I: Cognitive behavioural therapy (CBT), Acceptance and Commitment Therapy (ACT), Interpersonal Psychotherapy (IPT), Eye Movement Desensitization and Reprocessing (EMDR), psychological intervention, psycho-education.

C: Usual care, waiting list control, no intervention.

O: Fatigue (crucial), subjective cognitive complaints (crucial; memory and concentration problems) anxiety (crucial; including PTSD), depression (crucial), quality of life (important), return to work (important), sleep (important), adverse events (important)

Other selection criteria

Study design: systematic review and meta-analysis, randomized controlled trial, other comparative research.

Search update (September 2021): systematic reviews or randomized controlled trial

The databases Medline (via OVID) and Embase (via Embase.com) were searched with relevant search terms from 2019 up to and including May 4, 2021. The search was updated on September 7, 2021. The detailed search strategy is depicted under Methods (*Verantwoording*). Studies were selected based on the criteria as described in the PICO. The appendices (*Bijlagen*) contains the PRISMA flowcharts of the first search and the update, showing the number of hits, and the reasons of exclusion.

Relevant outcome measures

The working group defined the outcome measures as follows:

- Fatigue: as assessed using a validated fatigue questionnaire (e.g. Fatigue Severity Scale (FSS), Modified Fatigue Impact Scale (MFIS) or Checklist Individual Strength (CIS)).
- Subjective cognitive complaints: as assessed using a validated questionnaire (e.g. Cognitive Failure Questionnaire).
- Anxiety: as assessed using a validated questionnaire (e.g. Hospital Anxiety and Depression Scale (HADS-A)).
- Depression: As assessed using a validated depression questionnaire (e.g. Hospital Anxiety and Depression Scale (HADS-D)).
- Quality of Life: as determined with a validated quality of life questionnaire (e.g., 36-item Short Form Health Survey-36, EuroQol-5D).

The working group did not predefine the outcome measures return to work, sleep and adverse events, but used the definitions used in the included studies.

For all continuous outcomes, the working group defined 10% of the mean or median baseline value of the study groups as a minimal clinically (patient) important difference.

Given the huge variety in methods to determine and report adverse events, the working group did not a priori define the minimal clinically (patient) important difference for this outcome measure. The differences between the groups were evaluated by the working group after data extraction.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

Referenties

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Hyperbare zuurstoftherapie bij langdurige klachten na COVID-19

Uitgangsvraag

Wat is de waarde van hyperbare zuurstoftherapie voor patiënten met langdurige klachten na COVID-19?

Aanbeveling

Er is op dit moment onvoldoende bewijs om hyperbare zuurstoftherapie bij patiënten met langdurige klachten na COVID-19 aan te bevelen.

Indien in overleg met de patiënt gekozen wordt voor behandeling, doe dit dan in studieverband.

Overwegingen

Voor- en nadelen van de interventie en de kwaliteit van het bewijs

Er is literatuuronderzoek uitgevoerd naar de gunstige en ongunstige effecten van hyperbare zuurstoftherapie (*hyperbaric oxygen therapy*, HBOT) bij volwassen patiënten met langdurige klachten na COVID-19. Als cruciale uitkomstmaten werden kwaliteit van leven, fysiek functioneren/fysieke beperkingen en cognitief functioneren gedefinieerd, als belangrijke uitkomstmaten vermoeidheid, geheugen, aandacht, slaap, pijn en bijwerkingen. Er is één gerandomiseerd onderzoek gevonden dat 40 sessies hyperbare zuurstoftherapie (N=37) vergelijkt met een sham procedure (N=36). Er leek een klinisch relevant verschil te zijn in kwaliteit van leven in het domein van fysiek beperkingen. Er leken geen klinisch relevante verschillen te zijn in fysiek en cognitief functioneren. Een samenvattingsscore van fysieke en mentale kwaliteit van leven werd niet gerapporteerd. Voor de belangrijke uitkomstmaten geheugen, pijn, aandacht, angst en depressie leken er geen klinisch relevante verbeteringen te zijn na hyperbare zuurstoftherapie vergeleken met shambehandeling. Vermoeidheid en bijwerkingen werden niet of onvoldoende gerapporteerd. Op basis van de huidige literatuur lijkt er een gering effect van hyperbare zuurstoftherapie te zijn op korte termijn voor patiënten met langdurige klachten na COVID-19.

Het is van belang om op te merken dat, hoewel deze gerandomiseerde dubbelblinde klinische trial goed is uitgevoerd, er een zeer korte follow up duur van 3 weken is geweest. De interventietak van het onderzoek is na een jaar opgevolgd en de effecten bleken behouden (Hadanny, 2024). Helaas is er niet benoemd of de patiënten nog andere therapieën hebben gehad in deze periode.

De vraag is of de resultaten van de besproken studie toepasbaar zijn voor de patiëntengroep waar behandeling voor overwogen wordt, namelijk patiënten waarbij spontaan herstel dan wel herstel met primair paramedische begeleiding niet is opgetreden (duur van de klachten), en patiënten die ernstige beperkingen hebben in het dagelijks leven (ernst van de klachten). De studie includeerde patiënten met milde klachten van gemiddeld minder dan 6 maanden na COVID-19. Uit eerdere studies blijkt dat de meeste patiënten (>85%) binnen een jaar herstellen, daarna is de kans op herstel veel kleiner (Global Burden of Disease Long COVID Collaborators, 2022). In ongeveer 20% van de gevallen ervaren mensen door de aanhoudende klachten beperkingen ten aanzien van het vervullen van werk en sociale rollen. Mogelijk is dit percentage hoger bij patiënten die langdurig (>1 jaar) ziek zijn (Office for National Statistics, 2023). Daarmee lijken de patiënten met langdurige (>1 jaar ziek) en ernstige klachten (beperking in vervullen werk en/of sociale rollen)

mogelijk de meest relevante doelgroep die vanwege de ernst en/of complexiteit van de klachten verwezen zijn naar de medisch specialistische zorg. Op basis het huidige onderzoek is niet te zeggen wat de effecten van HBOT zijn in de relevante doelgroep zoals de expertisegroep die zou definiëren.

Eerdere (niet-placebo gecontroleerde) case reports en series tonen een positief effect van HBOT op cognitieve klachten en vermoeidheid. (Bhaiyat, 2022; Robbins, 2021). Ook werd daarbij een toename van doorbloeding van de hersenen, herstel van organisatie van neurale paden en toegenomen zuurstofconsumptie tijdens inspanning gerapporteerd (Bhaiyat, 2022; Catalogna, 2022). Ook verbeterde myocardiale functie door HBOT in langdurige klachten na COVID-19 (Leitman, 2023; in dezelfde populatie als Zilberman-Itskovich, 2022). Deze klinische en biomedische bevindingen, alsmede de aangetoonde effecten in andere aandoeningen en de huidige kennis over de pathofysiologische oorzaken van langdurige klachten na COVID-19, maken dat een mogelijk positief effect van HBOT niet uit te sluiten is. Om het gebruik van hyperbare zuurstoftherapie aan te bevelen dan wel af te raden, zal meer kwalitatief goed onderzoek verricht moeten worden in de relevante doelgroepen. Tot die tijd adviseert de expertisegroep om patiënten met langdurige klachten na COVID-19 alleen met HBOT te behandelen in studieverband.

Waarden en voorkeuren van patiënten (en evt. hun verzorgers)

Het is belangrijk te erkennen dat er een groep patiënten is die al langdurige ernstig beperkende klachten ervaren waar nog geen effectief bewezen behandeling voor is. Hyperbare zuurstoftherapie is een zeer intensieve therapie. Voor de beoogde doelgroep, patiënten met aanhoudende ernstige klachten na COVID-19, is het mogelijk te intensief om elke dag naar een locatie te komen en anderhalf tot 2 uur fysiologische stress te ervaren. In een interim veiligheid rapport van Kjellberg (2023) wordt specifiek genoemd dat maar een beperkt aantal patiënten met ernstige langdurige klachten na COVID-19, die deelnamen in de studiegroep, twee dagen achtereen HBOT konden verdragen door ernstige vermoeidheid. Voor patiënten met post-exertionele malaise (PEM) zou de behandeling bovendien tot een (tijdelijke) verergering van klachten kunnen leiden. Het risico op PEM zou derhalve moeten worden afgewogen tegen het mogelijke positieve effect van HBOT.

Kosten (middelenbeslag)

Hyperbare zuurstoftherapie is een kostbare therapie. Bij onvoldoende bewezen effectiviteit voor deze specifieke populatie zijn de hoge kosten een belemmerende factor om de therapie grootschalig in te zetten. De financiële baten (ten gevolge van bv minder ziekteverzuim, zorgconsumptie etc.) zijn nog onbekend.

Aanvaardbaarheid, haalbaarheid en implementatie

De therapie is aanvaardbaar omdat deze therapie al voor meerdere andere medische indicaties wordt toegepast. Er dient echter meer duidelijkheid te komen ten aanzien van of de patiënten met ernstige langdurige klachten na COVID-19 deze therapie kunnen verdragen, en wat het risico is van toename van de klachten in geval van aanwezigheid van PEM.

Er zijn slechts negen hyperbare kamers in Nederland, met een capaciteit van 10-20 personen per kamer en meerdere sessies per dag. De capaciteit en logistiek zijn op het moment van schrijven van de richtlijnmodule onvoldoende voor het behandelen van een grote groep patiënten met persisterende, langdurige klachten na COVID-19. Er is behoefte aan een RCT met patiënten die al langdurig ernstige klachten ervaren na COVID-

19, met de juiste metingen vooraf (waaronder cognitieve testen en immunologische markers en meenemen van de klacht vermoeidheid, PEM en dysautonomie) en met een langere follow-up om in te schatten of en voor wie hyperbare zuurstoftherapie zinvol en kosteneffectief is. Dit onderzoek zal multicenter en liefst internationaal moeten worden uitgevoerd. Dit is opgenomen in de post-COVID kennisagenda. Het meenemen van mitochondriële functie zou daarbij een waardevolle toevoeging zijn.

Rationale van de aanbeveling: weging van argumenten voor en tegen de interventies

Het huidige bewijs in relevante doelgroepen is op dit moment onvoldoende om hyperbare zuurstoftherapie aan te bevelen voor patiënten met langdurige klachten na COVID-19. Om het gebruik van hyperbare zuurstoftherapie aan te bevelen dan wel af te raden, zal meer kwalitatief goed onderzoek verricht moeten worden in de relevante doelgroepen. Indien in overleg met de patiënt toch gekozen wordt voor behandeling, dan adviseert de expertisegroep om patiënten met langdurige klachten na COVID-19 alleen met HBOT te behandelen in studieverband.

Onderbouwing

Achtergrond

Een deel van de COVID-19 patiënten blijft langer dan 3 maanden klachten houden na een doorgemaakte infectie. Hoewel studies verschillende afwijkingen laten zien bij patiënten met langdurige klachten na COVID-19, zoals een chronisch ontregeld afweersysteem, systemische chronische ontsteking van de bloedvaten en mogelijke aanwezigheid van kleine bloedstolsels in de bloedvaten, mitochondriële disfunctie en verhoogde oxidatieve stress, neurologische inflammatie, microbiomdysbiose, activatie van andere virussen en mogelijke persistentie van het virus of componenten hiervan in weefselreservoirs, wordt nog onvoldoende begrepen hoe dit precies ontstaat en met symptomen samenhangt (Davis, 2021).

Hyperbare zuurstoftherapie (*hyperbaric oxygen therapy*, HBOT) is een tweedelijns medische behandelmethode waarbij patiënten intermitterend 100% zuurstof inademen in een omgeving met een verhoogde luchtdruk van 2.0-2.5 bar totaal. De behandeling wordt uitgevoerd in een daarvoor specifiek ontworpen drukkamer/tank. Hieraan worden positieve effecten toegeschreven, onder andere verbetering van de doorbloeding door angio-neogenese, anti-inflammatoire effecten, herstel van mitochondriële functie en proliferatie en migratie van stamcellen (Fosen, 2014; Memar, 2019; Shinomiya, 2020). Gezien de vermoede onderliggende mechanismen van langdurige klachten na COVID-19, alsmede de toegeschreven effecten aan hyperbare zuurstoftherapie, is een mogelijk positief effect van hyperbare zuurstoftherapie te verwachten (Katz, 2024).

Conclusies / Summary of Findings

Critical outcome measures

Low GRADE	Hyperbaric oxygen therapy may result in improvement in health-related quality of life regarding physical limitations when compared to sham treatment in patients with persisting complaints after COVID-19. <i>Source: Zilberman-Itskovich, 2022</i>

Low GRADE	Hyperbaric oxygen therapy may result in little to no difference in health-related quality of life regarding physical function and cognitive function when compared to sham treatment in patients with persisting complaints after COVID-19. <i>Source: Zilberman-Itskovich, 2022</i>

No GRADE	No evidence was found regarding the effect of hyperbaric oxygen therapy on overall quality of life when compared to placebo/sham treatment in patients with persisting complaints after COVID-19.

Important outcome measures

Low GRADE	Hyperbaric oxygen therapy may result in little to no difference in memory, pain, attention, depression and anxiety when compared to sham treatment in patients with persisting complaints after COVID-19. <i>Source: Zilberman-Itskovich, 2022</i>

No GRADE	No evidence was found regarding the effect of hyperbaric oxygen therapy on fatigue/exhaustion and adverse events when compared to placebo/sham treatment in patients with persisting complaints after COVID-19.

Samenvatting literatuur

Description of studies

Zilberman-Itskovich (2022) reported results of a randomized, sham-control, double blind trial evaluating the effect of hyperbaric oxygen therapy (HBOT) in patients with persisting complaints after COVID-19. Patients ≥ 18 years old with reported post COVID-19 cognitive symptoms that affected their quality of life and persisted for more than three months following an RT-PCR test confirming a symptomatic SARS-CoV-2 infection were included. Patients were excluded if they had a history of pathological cognitive decline, traumatic brain injury or any other known non-COVID-19 brain pathology. Seventy-three patients were randomized to receive daily 40 session of HBOT ($n = 37$) or sham ($n = 36$). On average, patients in the two groups had post COVID-19 symptoms 159.1 ± 71.3 days and 171.5 ± 66.4 days. Limitations were overall mild, given the baseline quality of life scores and the full-time employment status of over 60% of participants. Both HBOT and sham protocols were administrated in a multi-place Starmed-2700 chamber (HAUX, Germany). The protocol comprised of 40 daily sessions, five sessions per week within a two-month period. The HBOT protocol included breathing 100% oxygen by mask at 2ATA for 90 min with five-minute air breaks every 20 min. Compression/decompression rates were 1.0 m/min. The sham protocol included breathing 21% oxygen by mask at 1.03 ATA for 90 min. To mask the controls, the chamber pressure was raised up to 1.2 ATA during the first five minutes of the session along with circulating air noise followed by decompression (0.4 m/min) to 1.03 ATA during the next five minutes. Follow-up assessments were performed at baseline and 1–3 weeks after the last treatment session. The primary outcome of the study was the cognitive assessment as evaluated by the

Mindstreams computerized cognitive testing battery (NeuroTrax Corporation, Bellaire, TX). Secondary outcomes included MRI-based outcomes, quality of life, sleep quality, psychological distress and pain. The risk of bias was considered low.

Results

Results of the reported outcome measures are summarized in table 1.

Table 1. Reported outcomes

Outcome measure	Instrument	Post-treatment score	Change from baseline	Clinically relevant
Cognitive function	Mindstreams computerized cognitive testing battery; each outcome parameter was normalized and fit to an IQ-like scale (mean: 100, SD: 15)	HBOT: 104.1 ± 7.2 Sham: 101.3 ± 8.9	HBOT: 5.8 ± 7.9 Sham: 2.4 ± 5.4	No
Physical function	Subset from SF-36; 0-100 scale, lower scores denote more disability	HBOT: 63.0 ± 29.3 Sham: 58.6 ± 26.9	HBOT: 2.7 ± 21.0 Sham: 7.9 ± 17.5	No
Physical limitations	Subset from SF-36; 0-100 scale, lower scores denote more limitations	HBOT: 50.7 ± 38.3 Sham: 38.9 ± 38.8	HBOT: 33.8 ± 40.9 Sham: 9.7 ± 47.2	Yes
Memory	Subset from Mindstreams computerized cognitive testing battery; IQ-like scale (mean: 100, SD: 15)	HBOT: 102.0 ± 10.9 Sham: 102.1 ± 8.7	HBOT: 8.3 ± 11.2 Sham: 7.2 ± 8.5	No
Pain	Brief pain inventory (short form); pain severity 0-10, higher scores denote more pain	HBOT: 1.4 ± 2.5 Sham: 1.3 ± 2.2	HBOT: - 0.2 ± 1.8 Sham: - 0.1 ± 2.3	No
Attention	Subset from Mindstreams computerized cognitive testing battery; IQ-like scale (mean: 100, SD: 15)	HBOT: 101.9 ± 9.0 Sham: 99.4 ± 10.1	HBOT: 4.6 ± 12.4 Sham: - 0.3 ± 8.3	No
Depression	Subset from Brief Symptom Inventory (BSI-18), 0-24, higher scores denote more depression	HBOT: 4.1 ± 4.7 Sham: 5.6 ± 6.3	HBOT: - 3.2 ± 5.4 Sham: - 0.8 ± 4.4	No
Anxiety	Subset from Brief Symptom Inventory (BSI-18), 0-24, higher scores denote more anxiety	HBOT: 5.9 ± 4.7 Sham: 7.2 ± 6.3	HBOT: - 2.5 ± 4.5 Sham: - 0.5 ± 5.3	No
Somatization	Subset from Brief Symptom Inventory (BSI-18), 0-24, higher scores denote more anxiety	HBOT: 6.2 ± 5.9 Sham: 7.7 ± 5.5	HBOT: - 3.1 ± 3.8 Sham: 7.7 ± 5.5	No

For quality of life, results of the SF-36 subsets were reported, but no physical component score (PCS) and mental component score (MCS) was presented. Also fatigue/exhaustion was not reported. The evidence for

these outcomes could not be graded.

Regarding adverse events of the treatment, 13 events were reported in the HBOT group versus 14 in the control group (table 2). These results were not reported at patient level, therefore the evidence could not be graded.

Table 2. Adverse events

Adverse event	HBOT	Sham
Barotrauma	4	3
Ear pain without barotrauma	1	0
Palpitation	3	1
Allergic rash	0	1
Headache	1	0
Emergency referral secondary to chest pain / epigastric pain	1	2
Fever	1	1
Urinary tract infection	0	2
Hospitalization due to herpes zoster infection	1	0
Cellulitis requiring antibiotic treatment	0	1
Pre-syncope	0	1
Hypertension	1	0
Pregnancy	0	1
Emotional distress with psychological intervention	0	1
Total	13	14

Level of evidence of the literature

The level of evidence regarding all outcome measures was based on a randomized controlled study and therefore started at high.

The level of evidence for physical function/limitations, cognitive function, memory, attention, sleep and pain were downgraded by 2 levels to LOW due to the limited number of included patients (imprecision, -2).

The level of evidence for the outcome measures overall quality of life, fatigue/exhaustion and adverse events could not be graded due to a lack of data.

Zoeken en selecteren

A systematic review of the literature was performed to answer the following question:

What are the benefits and harms of hyperbaric oxygen therapy for patients with persisting complaints after COVID-19?

P: Patients with persisting complaints after COVID-19 (post COVID-19 condition)

I: Hyperbaric oxygen therapy

C: Placebo/sham

O: Quality of life, physical function/limitations, cognitive function, fatigue/exhaustion (including post-exertional malaise), memory, attention, pain, anxiety/depression, adverse events.

Relevant outcome measures

In line with the international Delphi study by Munblit (2022), which defined a core outcome set for post COVID-19 condition in adults, the guideline development group considered quality of life, physical function/limitations and cognitive function as critical outcome measures for decision making; and fatigue/exhaustion, memory, attention, sleep, pain and adverse events as important outcome measures for decision making.

The working group did not define the outcome measures listed above a priori, but followed the definitions used in the studies. With regard to the study population, patients with persisting complaints for at least three months after SARS-CoV-2 infection were considered.

The working group defined a between-group difference of 10% of the maximum score as a minimal clinically (patient) important difference for continuous outcome measures.

Search and select (Methods)

The databases Embase.com and Ovid/Medline were searched with relevant search terms until October 30, 2023. The detailed search strategy is depicted under the tab Methods. The systematic literature search resulted in 54 hits. Studies were selected based on the following criteria: prospective intervention studies comparing hyperbaric oxygen therapy plus standard of care with standard of care only in patients with persisting complaints/symptoms for at least 3 months after COVID-19. To obtain the highest level of evidence, observational studies were excluded once a randomized trial was found. Nine studies were initially selected based on title and abstract screening. After reading the full text, eight studies were excluded (see the table with reasons for exclusion under the tab Methods), and one publication was included.

Results

One randomized trial was included in the analysis of the literature. Important study characteristics and results are summarized in the evidence tables. The assessment of the risk of bias is summarized in the risk of bias tables.

Verantwoording

Laatst beoordeeld : 20-09-2024

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijnendatabase.

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Multidisciplinaire zorg na COVID-19

Uitgangsvraag

Hoe kan de multidisciplinaire behandeling van langetermijnklachten na COVID-19 worden vormgegeven?

Aanbeveling

Overweeg multidisciplinaire behandeling in de eerste lijn bij matig ernstige samenhangende klachten die ≥ 6 weken na COVID-19 aanhouden, waarbij op basis van de gestelde doelen interventies op elkaar worden afgestemd en zo nodig (gezamenlijk) worden geëvalueerd. Maak hierbij zoveel mogelijk gebruik van bestaande samenwerkingsverbanden.

Bepaal in onderling overleg wie de zorg coördineert. In de eerste lijn zal dit vaak de huisarts zijn. De coördinerend zorgverlener houdt overzicht over de behandeling in de eerste lijn en signaleert stagnatie van herstel.

Overweeg verwijzing naar de tweede lijn voor een multidisciplinair overleg bij:

- onvoldoende herstel van matig ernstige samenhangende klachten na ≥ 6 maanden behandeling in de eerste lijn; of
- grote complexiteit van klachten; of
- diagnostische twijfel of de combinatie van klachten en het beloop passend zijn bij herstel na COVID-19

Benader, indien regionaal beschikbaar, voor verwijzing het aanspreekpunt of verwijzingsloket voor het multidisciplinaire overleg binnen het betreffende ziekenhuis (zie de module [Multidisciplinair overleg](#)).

Overwegingen

Bij langdurige klachten na een COVID-19-infectie kunnen problemen op meerdere fronten spelen, waardoor de inzet van meerdere zorgprofessionals gewenst is. Hoewel bij mildere klachten verwijzing naar een specifieke zorgprofessional vaak volstaat, is met name bij ernstigere klachten of klachten op meerdere domeinen verwijzing naar meerdere zorgprofessionals nodig.

Hierbij worden de 'stepped-care'-principes gevolgd; de behandeling is niet intensiever dan nodig en complexere interventies komen pas in beeld als eenvoudige interventies onvoldoende resultaat hebben.

Multidisciplinaire behandeling

Het multidisciplinair beleid is afhankelijk van de ernst, duur en complexiteit van de klachten.

Indien meerdere zorgprofessionals betrokken zijn bij de zorg voor een patiënt, is het belangrijk om op basis van de gestelde doelen de interventies op elkaar af te stemmen en zo nodig (gezamenlijk) te evalueren.

Hierbij wordt bij voorkeur gebruik gemaakt van bestaande samenwerkingsverbanden. Overweeg bestaande samenwerkingsverbanden te optimaliseren en daar waar nog geen regionale samenwerkingsverbanden tot stand zijn gekomen deze te initiëren.

Coördinatie van zorg

Bepaal in onderling overleg wie de multidisciplinaire behandeling coördineert. In de eerste lijn is dit vaak de

huisarts. Deze houdt overzicht over alle bij de behandeling betrokken eerstelijns zorgprofessionals en signaleert stagnatie van herstel. Zo nodig kunnen ook andere eerstelijns zorgprofessionals de coördinatie van de zorg op zich nemen.

Betrokken zorgprofessionals zijn zelf verantwoordelijk voor onderlinge afstemming over de behandeldoelen en evaluatie van het ingezette beleid. Goede communicatie over de voortgang van de behandeling is hierbij van belang. Mocht het ingezette beleid onvoldoende blijken, dan is het aan de signalerende zorgprofessional hiernaar te handelen. Na overleg met de patiënt kunnen indien nodig in overleg met en op verwijzing van de behandelend huisarts andere zorgprofessionals bij de behandeling betrokken worden. De signalerend zorgprofessional stelt hiervan ook de coördinerend zorgprofessional op de hoogte.

In de tweede lijn wordt een regiebehandelaar (voorheen hoofdbehandelaar) aangewezen die toeziet op de continuïteit en samenhang van de zorg, en een adequate informatie-uitwisseling naar andere zorgprofessionals. Het is van belang dat de patiënt weet wie zijn aanspreekpunt is.

Multidisciplinair overleg

De huisarts overweegt verwijzing naar de tweede lijn in de volgende gevallen:

- bij onvoldoende herstel van matig ernstige samenhangende klachten na ≥ 6 maanden behandeling in de eerste lijn
- bij grote complexiteit van klachten
- bij diagnostische twijfel of de combinatie van klachten en het beloop passend zijn bij herstel na COVID-19

Indien een multidisciplinair overleg beschikbaar is, kan voor verwijzing het aanspreekpunt of verwijsloket voor het multidisciplinaire overleg binnen het betreffende ziekenhuis benaderd worden (zie de module Multidisciplinair overleg). Het vervolgbeleid wordt op basis van de uitkomsten van het multidisciplinair overleg bepaald. De revalidatiearts en de specialist ouderengeneeskunde, beiden bij voorkeur vertegenwoordigd in het multidisciplinair overleg, stellen de indicatie voor respectievelijk medisch-specialistische revalidatie (MSR) en geriatrische revalidatiezorg (GRZ). Hiervoor komt een selecte groep in aanmerking (zie voor indicaties de module Indicatiestelling revalidatietraject en hertriage bij COVID-19; VRA en Verenso, 2021).

Multidisciplinair overleg waar patiënten met langdurige klachten na COVID-19 worden besproken in de tweede lijn is nog niet overal gerealiseerd. Verwijs in dit geval naar de meest voor de hand liggende medisch specialist, afhankelijk van de meest beperkende langdurige klacht.

We verwijzen ook naar de module Arbeid, voor de rol van de bedrijf- en verzekeringsarts bij werk(hervatting) en/of aangepast werk. Zorgverleners kunnen ook een beroep doen op C-support ter ondersteuning of advisering. Deze netwerkorganisatie ondersteunt mensen met > 3 maanden (complexe) klachten na COVID-19.

Onderbouwing

Achtergrond

Klachten in de eerste 4 weken na de SARS-CoV-2-infectie behoren bij de acute fase van de infectie. Deze richtlijn richt zich op patiënten die ≥ 4 weken klachten hebben. In deze richtlijn zijn een groot aantal mogelijke interventies onderzocht. Deze module gaat specifiek over de behandeling van patiënten met meerdere, samenhangende klachten na COVID-19. Patiënten met een enkelvoudige klacht vallen niet onder deze module.

Zoeken en selecteren

We did not perform a systematic search for the current module. The 'Overwegingen/Van bewijs naar aanbevelingen' (evidence to decision) and the recommendations are based on the conclusions and recommendations in the previous modules, for which search strategies and literature summaries are available.

Verantwoording

Laatst beoordeeld : 21-03-2022

Voor de volledige verantwoording, evidence tabellen en eventuele aanverwante producten raadpleegt u de Richtlijndatabase.

Referenties

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