Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

und

Schriftliche Beteiligung der wissenschaftlich-medizinischen Fachgesellschaften und der Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ) zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Tixagevimab/Cilgavimab

Stand: Juli 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA

Tixagevimab/Cilgavimab Behandlung von COVID-19 **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Remdesivir, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 16. September 2021 - Remdesivir, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 7. Juli 2022
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet**
Zu bewertendes Arzneimittel:	
Tixagevimab/ Cilgavimab J06BD03 EVUSHELD®	Anwendungsgebiet laut Zulassung: EVUSHELD wird angewendet zur Behandlung einer Coronavirus-19-Erkrankung bei Erwachsenen und Jugendlichen (ab 12 Jahren mit mindestens 40 kg Körpergewicht), die keine zusätzliche Sauerstoffzufuhr benötigen und bei denen ein erhöhtes Risiko für einen schweren Verlauf von COVID-19 besteht.
Dexamethason H02AB02 Dexa inject JENAPHARM®	Dexa 4/8/40/100 mg inject JENAPHARM wird angewendet zur Behandlung der Coronavirus-Krankheit 2019 (COVID-19) bei Erwachsenen und Jugendlichen (im Alter von mindestens 12 Jahren und mit einem Körpergewicht von mindestens 40 kg), die eine zusätzliche Sauerstoffzufuhr erfordert.
Remdesivir J05AB16 Veklury®	Veklury wird angewendet zur Behandlung der Coronavirus-Krankheit 2019 (COVID-19) bei: - Erwachsenen und Jugendlichen (im Alter von 12 bis unter 18 Jahren und mit einem Körpergewicht von mindestens 40 kg) mit einer Pneumonie, die eine zusätzliche Sauerstoffzufuhr erfordert (Low- oder High-Flow Sauerstofftherapie oder eine andere nicht-invasive Beatmung zu Therapiebeginn) - Erwachsenen, die keine zusätzliche Sauerstoffzufuhr benötigen und ein erhöhtes Risiko haben, einen schweren COVID-19-Verlauf zu entwickeln.
Regdanvimab N/N Regkirona®	Regdanvimab wird angewendet zur Behandlung von Erwachsenen mit bestätigter Coronavirus-2019-Erkrankung (COVID-19), die keine Sauerstoffsubstitution benötigen und ein erhöhtes Risiko für einen schweren Verlauf der COVID-19-Erkrankung haben.
Casirivimab/ Imdevimab N/N Ronapreve®	- Behandlung einer Coronavirus-2019-Erkrankung (COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht, die keine zusätzliche Sauerstofftherapie benötigen und bei denen ein erhöhtes Risiko für einen schweren Verlauf von COVID-19 besteht. - Prophylaxe von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Anakinra L04AC03 Kineret®	Kineret wird angewendet zur Behandlung der Coronavirus-Krankheit 2019 (COVID-19) bei Erwachsenen mit einer Pneumonie, die eine zusätzliche Sauerstoffzufuhr (Low- oder High-Flow-Sauerstofftherapy) benötigen und bei denen das Risiko für eine Progression zu einer schweren respiratorischen Insuffizienz besteht, bestimmt anhand einer Plasmakonzentration des löslichen Urokinase-Plasminogen-Aktivator-Rezeptors (suPAR) von ≥ 6 ng/ml.
Tocilizumab L04AC07 RoActemra®	RoActemra ist zur Behandlung einer Coronavirus-2019-Erkrankung (COVID-19) bei Erwachsenen angezeigt, die systemische Corticosteroide erhalten und eine zusätzliche Sauerstofftherapie oder maschinelle Beatmung benötigen.
Nirmatrelvir/ Ritonavir N/N Paxlovid®	Paxlovid wird angewendet zur Behandlung einer Coronavirus-Krankheit 2019 (COVID-19) bei Erwachsenen, die keine zusätzliche Sauerstoffzufuhr benötigen und ein erhöhtes Risiko haben, einen schweren COVID-19-Verlauf zu entwickeln.
Sotrovimab J06BD Xevudy®	Xevudy ist zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 40 kg) mit einer Coronavirus-Krankheit-2019 (coronavirus disease 2019, COVID-19) indiziert, die keine Sauerstoff-Supplementierung benötigen und ein erhöhtes Risiko für einen schweren Krankheitsverlauf von COVID-19 haben.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V

Vorgang: Tixagevimab/Cilgavimab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	12.04.2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

ARDS	Acute Respiratory Distress Syndrome
AWMF	Arbeitsgemeinschaft derwissenschaftlichen medizinischen Fachgesellschaften
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
ECMO	Extracorporeal Mechanical Oxygenation
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development and Evaluation
HFNC	High-Flow Nasal Cannula
HR	Hazard Ratio
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IMV	invasive mechanical ventilation
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MAGICapp	Making GRADE the Irresistible Choice
MD	Mean Difference
MERS	Middle East Rrespiratory Syndrome
nCOV-2019	novel Coronavirus-2019
NICE	National Institute for Health and Care Excellence
NIPPV	Non-Invasive Positive Pressure Ventilation
NMBA	Neuromuscularblocking agents
OR	Odds Ratio
PEEP	Positive Endexpiratory Pressure
Ppla	Plateau pressures
RCT	Randomized Controlled Trial
ROB-2	Risk of bias tool 2
ROBINS-I	Risk of Bias Instrument for Non-randomized Studies – of Interventions
RR	Relatives Risiko
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
SpO2	percentage of oxyhemoglobin saturation
SSC	Surviving Sepsis Campaign
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von COVID-19

Hinweise zur Synopse:

- Remdesivir, Dexamethason, Casirivimab/Imdevimab, Regdanvimab, Sotrovimab, Anakinra und Tocilizumab sind zum Zeitpunkt der Erstellung der vorliegenden Synopse zugelassene Medikamente in Deutschland. Identifizierte Quellen zu diesen Wirkstoffen sind sowohl im Kapitel der systematischen Reviews, als auch im Kapitel der Leitlinien dargestellt.
- Informationen hinsichtlich nicht zugelassener Therapieoptionen sind primär über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation Indikation COVID-19 durchgeführt und nach PRISMA-S dokumentiert [A]. Die Recherchestrategie wurde vor der Ausführung anhand der PRESS-Checkliste begutachtet [B]. Es erfolgte eine Datenbankrecherche ohne Sprachrestriktion in: The Cochrane Library (Cochrane Database of Systematic Reviews), PubMed. Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 09.02.2021 durchgeführt, die folgenden am 06.09.2021 und 01.04.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 4761 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 42 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Ansems K et al., 2021 [3].
Remdesivir for the treatment of COVID-19 (Review)

Fragestellung

To assess the effects of remdesivir compared to placebo or standard care alone on clinical outcomes in hospitalised patients with SARSCoV-2 infection, and to maintain the currency of the evidence using a living systematic review approach.

Methodik

Population:

- Hospitalised adults with confirmed SARS-CoV-2 infection

Intervention:

- remdesivir

Komparator:

- placebo or standard care alone

Endpunkte:

- All-cause mortality at up to day 28, day 60, time-to-event, and at hospital discharge.
- Clinical status, assessed by need for respiratory support with standardised scales (e.g. WHO Clinical Progression Scale (WHO 2020d), WHO Ordinal Scale for Clinical Improvement (WHO 2020d) at up to day 28, day 60, and up to longest followup), including:
  - improvement of clinical status: liberation from invasive mechanical ventilation in surviving participants; ventilator-free days; duration to liberation from invasive mechanical ventilation; liberation from supplemental oxygen in surviving participants; duration to liberation from supplemental oxygen.
  - worsening of clinical status: new need for mechanical ventilation (defined as high-flow oxygen, non-invasive, or invasive mechanical ventilation); new need for invasive mechanical ventilation; new need for non-invasive mechanical ventilation or highflow oxygen; new need for oxygen by mask or nasal prongs.
- Need for dialysis at up to day 28.
- Quality of life, including fatigue and neurological status, assessed with standardised scales (e.g. WHOQOL-100) at up to seven days, up to 30 days, and longest follow-up available.
- Need for admission to ICU
- Duration of ICU length of stay, or time to discharge from ICU.
- Duration of hospitalisation, or time to discharge from hospital.
- Viral clearance, assessed with reverse transcription polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to 3, 7, and 15 days.
- Serious adverse events and adverse events

Recherche/Suchzeitraum:

- We searched the Cochrane COVID-19 Study Register (which comprises the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed,Embase, ClinicalTrials.gov, WHO International Clinical Trials Registry Platform,and medRxiv) as well as Web of Science (Science Citation Index Expanded and Emerging Sources Citation Index) and WHO COVID-19 Global literature on coronavirus disease to identify completed and ongoing studies without language restrictions. We conducted the searches on 16 April 2021.

Qualitätsbewertung der Studien:

- Risk of bias (RoB 2) tool, Grading of Recommendations Assessment, Development, and Evaluation (GRADE)

Ergebnisse

Anzahl eingeschlossener Studien:

- five RCTs with 7452 participants diagnosed with SARS-CoV-2 infection in the review (Beigel 2020; Spinner 2020; Wang 2020; Mahajan 2021; WHO Solidarity Trial Consortium 2021).

Charakteristika der Population:

Table 3. Overview of included studies

	Beigel 2020 [a]	Spinner 2020	Wang 2020	WHO Solidarity Trial Consortium 2021	Mahajan 2021
	(By date of publication)				
Setting	• Inpatient • Multinational	• Inpatient • Multinational	• Inpatient • China	• Inpatient • Multinational	• Inpatient • India
Design	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Double-blind • Placebo-controlled	• Randomised • Open-label • Controlled	• Randomised • Open-label • Controlled
Study protocol	Reported	Reported	Reported	Reported	Not reported
Statistical analysis plan	Reported	Reported	Reported	Reported	Not reported
Intervention (remdesivir) **(duration of application (days))**	10	5 or 10	10	10	5
Control	SoC	Placebo + SoC	Placebo + SoC	SoC	SoC
Allocated participants (n)	1062	596	236	5475	82
Number of participants per trial arm (allocated/evaluated)	Intervention: 541/541 Placebo + SoC: 521/521	5-day intervention: 199/191 10-day intervention: 197/193 SoC: 200/200	Intervention: 158/158 Placebo + SoC: 78/78	Intervention: 2750/2743 SoC: 2725/2708	Intervention: 41/34 SoC: 41/36

Qualität der Studien:

- risk of bias siehe Anhang Abbildung 2

Studienergebnisse:

Remdesivir compared to placebo or standard care alone for hospitalised adults with confirmed SARS-CoV-2 infection

Patient or population: hospitalised adults with confirmed SARS-CoV-2 infection
Settings: in-hospital
Intervention: remdesivir (10 days)
Comparator: placebo or standard care alone

Outcomes	Anticipated absolute effects		Relative effect 95% CI	No. of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Assumed risk					
	Placebo or standard care alone	Risk difference with remdesivir				
All-cause mortality at up to day 28	108 per 1000[i]	8 fewer per 1000 (21 fewer to 7 more)	RR 0.93 (0.81 to 1.06)	7142 (4 RCTs)	⊕⊕⊕⊖ MODERATE Due to serious imprecision[1]	Remdesivir probably makes little or no difference to all-cause mortality.
Improvement of clinical status: duration to liberation from invasive mechanical ventilation at up to day 28	2 studies reported this outcome as median, which could not be included in meta-analysis. 1 study reported a median of 17 days (IQR 9 to 28) in the remdesivir group and 20 days (IQR 8 to 28) in the control group (rate difference −3.0, 95% CI −9.3 to 3.3). The other study reported a median of 7 days (IQR 4 to 16) in the remdesivir group and 15.5 days (IQR 6 to 21) in the control group (rate difference −4.0, 95% CI −14 to 2).			1298 (2 RCTs)	⊕⊕⊖⊖ LOW Due to serious risk of bias and serious imprecision[2,3]	Remdesivir may have little or no effect on improvement of clinical status: duration to liberation from invasive mechanical ventilation.
Improvement of clinical status: duration to liberation from supplemental oxygen at up to day 28	3 studies reported this outcome as median, which could not be included in meta-analysis. 1 study reported a median of 13 days (IQR 5 to 28) in the remdesivir group and 21.0 days (IQR 8 to 28) in the control group (rate difference −8.0, 95% CI −11.8 to -4.2). 1 study reported a median of 19 days (IQR 11 to 30) in the remdesivir and 21 days (IQR 14 to 30.5) in the control group (rate difference −2, 95% CI −6 to 1). The third study reported time to room air regardless of the initial respiratory support: 4 days (IQR 2 to 6) in the remdesivir group and 6 days (IQR 4 to 14) in the control group (HR 1.93, 95% CI 1.11 to 3.36).			1691 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious imprecision, and other considerations[2,4,5]	We are uncertain as to whether remdesivir increases or decreases the chance of clinical improvement: duration to liberation from supplemental oxygen .

Clinical worsening: new need for mechanical ventilation at day 28 (defined as high-flow oxygen, non-invasive, or invasive mechanical ventilation)	131 per 1000	29 fewer per 1000 (68 fewer to 32 more)	RR 0.78 (0.48 to 1.24)	6696 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious imprecision, and serious inconsistency[1,4,6]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for mechanical ventilation.
Clinical worsening: new need for invasive mechanical ventilation at up to day 28	152 per 1000	67 fewer per 1000 (90 fewer to 35 fewer)	RR 0.56 (0.41 to 0.77)	1159 (2 RCTs)	⊕⊕⊖⊖ LOW Due to serious risk of bias and other considerations[4,5]	Remdesivir may decrease the risk of clinical worsening: new need for invasive mechanical ventilation.
Clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen at up to day 28	241 per 1000	72 fewer per 1000 (118 fewer to 5 fewer)	RR 0.70 (0.51 to 0.98)	573 (1 RCT)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias and very serious imprecision[3,7]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for non-invasive mechanical ventilation or high-flow oxygen.
Clinical worsening: new need for oxygen by mask or nasal prongs at up to day 28	444 per 1000	84 fewer per 1000 (204 fewer to 98 more)	RR 0.81 (0.54 to 1.22)	138 (1 RCT)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias and very serious imprecision[3,8]	We are very uncertain as to whether remdesivir decreases or increases the risk of clinical worsening: new need for oxygen by mask or nasal prongs.
Quality of life	NA	NA	NA	NA	NA	None of the included studies reported quality of life, therefore we do not know whether remdesivir has any impact on this outcome.
Serious adverse events at up to day 28	253 per 1000	63 fewer per 1000 (94 fewer to 25 fewer)	RR 0.75 (0.63 to 0.90)	1674 (3 RCTs)	⊕⊕⊕⊖ MODERATE Due to serious risk of bias[3]	Remdesivir probably decreases the risk of serious adverse events.
Adverse events (any grade) at up to day 28	587 per 1000	29 more per 1000 (82 fewer to 158 more)	RR 1.05 (0.86 to 1.27)	1674 (3 RCTs)	⊕⊖⊖⊖ VERY LOW Due to serious risk of bias, serious inconsistency, and serious imprecision[1,3,9]	We are very uncertain as to whether remdesivir increases or decreases adverse events (any grade).

CI: confidence interval; **HR:** hazard ratio; **IQR:** interquartile range; **NA:** not applicable; **RCT:** randomised controlled trial; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: We are very confident that the true effect lies close to that of the estimate of effect.
Moderate certainty: We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: Our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

i. All-cause mortality at hospital discharge: RR 0.98, 95% CI 0.84 to 1.14; 1 study, 5451 participants; I^2 not applicable. All-cause mortality (time-to-event): HR 0.93, 95% CI 0.80 to 1.07; 2 studies, 6513 participants; $I^2 = 57\%$.
[1]Downgraded one level due to serious imprecision because of wide confidence intervals in the studies and the 95% confidence interval includes both benefits and harms.
[2]Downgraded one level due to serious imprecision because the 95% confidence interval includes both benefits and harms.
[3]Downgraded one level due to serious risk of bias because of competing risk of death.
[4]Downgraded one level due to serious risk of bias because of inadequate blinding of participants, personnel, and outcome assessors and possible deviation in time point of measuring in one study, and competing risk of death.
[5]Downgraded one level due to other considerations, as studies reported outcomes differently because of missing standards.
[6]Downgraded one level due to serious inconsistency because of statistical heterogeneity ($I^2 = 85\%$).
[7]Downgraded two levels due to serious imprecision because of few participants and data from only one study.
[8]Downgraded two levels due to very serious imprecision because of wide confidence intervals and data from only one study.
[9]Downgraded one level due to serious inconsistency because of statistical heterogeneity ($I^2 = 77\%$).

- There was limited evidence for a beneficial effect of remdesivir on mortality in a subset of 435 participants who received low flow oxygen at baseline in one study (RR 0.32, 95% CI 0.15 to 0.66). We could not confirm this finding due to restricted availability of relevant subgroup data from other studies.

Anmerkung/Fazit der Autoren

We found moderate-certainty evidence that remdesivir probably has little or no effect on all-cause mortality at up to 28 days in hospitalised individuals with moderate and severe COVID-19. We were unable to perform meta-analysis of clinical improvement parameters, but

considering the data provided, remdesivir may have little or no effect on the duration to liberation from invasive mechanical ventilation. We are uncertain whether remdesivir increases or decreases the chance of clinical improvement in terms of duration to liberation from supplemental oxygen at up to day 28 given the very low certainty of the evidence. We found low-certainty evidence that remdesivir may decrease the risk of new need for invasive mechanical ventilation. However, we are very uncertain whether remdesivir affects the overall risk for clinical worsening. There were insufficient data available to examine the effect of remdesivir on mortality across subgroups defined by respiratory support at baseline. Remdesivir probably decreases the rate of serious adverse events; however, due to inconsistent reporting of safety data, the evidence regarding the effect of remdesivir is very uncertain when pooling any grade of adverse events. Due to incompleteness of subgroup data, we are uncertain whether there is a possible benefit of remdesivir for the treatment of COVID-19 patients receiving lowflow oxygen therapy only.

Kommentare zum Review

SR mit vergleichbarer Methodik und vergleichbaren Ergebnissen

- Tanni SE et al., 2022 [34]. Use of remdesivir in patients with COVID-19: a systematic review and meta-analysis.
  - Im Vergleich zu Ansems et al., konnte eine weitere Studie gefunden werden, die Studie von Ader et al. mit knapp über 800 Teilnehmenden.
  - Es zeigte sich kein Vorteil bei OS
  - Es wurde ein statistisch signifikanter Vorteil von Remdesevir bei clinical recovery gezeigt
  - Ein Vorteil bei SUE wurde anders als in Ansems et al. nicht gezeigt. Dies liegt vermutlich maßgeblich an der Hinzunahme der Studie von Ader et al.
- Al-Abdouh A et al., 2021 [2]. Remdesivir for the treatment of COVID-19: A systematic review and meta-analysis of randomized controlled trials.
  - Zusätzlich wurde statistisch signifikanter Vorteil von Remdesevir bei clinical recovery gezeigt („Patients were considered to be recovered in our study if they were discharged alive from the hospital or were admitted without oxygen requirements (for infection control purposes)"
- Singh S et al., 2021 [31]. Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis.
  - Zusätzlich wurde statistisch signifikanter Vorteil von Remdesevir bei clinical recovery gezeigt
- Verdugo-Paiva F et al., 2021 [38]. Remdesivir for the treatment of COVID-19: a living systematic review.
- Kaka AS et al., 2021 [17]. Major Update: Remdesivir for Adults With COVID-19 : A Living Systematic Review and Meta-analysis for the American College of Physicians Practice Points
- Juul S et al., 2021 [16]. Interventions for treatment of COVID-19: Second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project)
- Okoli GN et al., 2021 [27]. Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials.

Davidson M et al., 2022 [10].

Interleukin-1 blocking agents for treating COVID-19.

Fragestellung

To assess the ePects of IL-1 blocking agents compared with standard care alone or with placebo on effectiveness and safety outcomes in people with COVID-19.

This review is part of a larger project: the COVID network meta-analysis (COVID-NMA) initiative (Boutron 2020a). The COVIDNMA initiative provides decision-makers with a complete, high-quality and up-to-date mapping and synthesis of evidence on interventions for preventing and treating COVID-19. We developed a master protocol on the effect of all interventions for preventing and treating COVID-19 (Boutron 2020b) and a specific protocol for IL-1 blocking agents detailed in the methods section. Our results are made available and updated weekly on the COVID-NMA platform at covid-nma.com.

This living review focuses on SARS-CoV-2 and does not consider studies evaluating treatment with IL-1 blocking agents for other coronavirus infections affecting humans.

Methodik

Population:

- children or adults with suspected, probable, or confirmed COVID-19

Intervention:

- anakinra (interleukin-1 receptor antagonist);
- canakinumab (human anti-IL-1\ monoclonal antibody);
- rilonacept (interleukin-1 blocker)

➢ Aufgrund des Zulassungsstatus werden nur die Ergebnisse von Anakinra dargestellt

Komparator:

- standard care alone or with placebo;
- standard of care as defined by trialists.

Endpunkte:

- Clinical improvement (D28/ ≥ D60) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery.
- WHO Clinical Progression Score of level 7 or above (i.e. mechanical ventilation +/- additional organ support (extracorporeal membrane oxygenation (ECMO), vasopressors or dialysis) or death (D28/ ≥ D60).
- All-cause mortality (D28/ ≥ D60).
- (Serious) adverse events (S)(AEs)
- Time to clinical improvement
- Time to WHO Clinical Progression Score of level 7 or above
- Time to death

Recherche/Suchzeitraum:

- We searched the following databases on 5 November 2021.
  - The L-OVE platform (app.iloveevidence.com/covid19), every working day since 7 September 2020.
  - The Cochrane COVID-19 Study Register (covid-19.cochrane.org/), weekly since 7 September 2020.
- Weitere bis 3 November 2021.

Qualitätsbewertung der Studien:

- Cochrane Risk of Bias 2 (RoB 2)

Ergebnisse

Anzahl eingeschlossener Studien:

- We included seven reports of six RCTs (five published in peer-reviewed journals and one reported as a preprint) evaluating IL-1 blocking agents. Four RCTs evaluated anakinra (Declercq COVAID 2021; Derde REMAP-CAP 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021), and two evaluated canakinumab (Caricchio CAN-COVID 2021; Cremer Three C Study 2021).

Charakteristika der Population:

- four RCTs, 1633 randomised participants assessing anakinra
- Participants had moderate disease (Mariette CORIMUNO-19 Collaborative 2021), mild to severe disease (Kyriazopoulou SAVE-MORE 2021), moderate to critical disease (Declercq COV-AID 2021), severe to critical disease (Derde REMAP-CAP 2021).
- The percentage of participants on oxygen at baseline but not intubated was respectively 67% (Derde REMAP-CAP 2021), 87% (Declercq COV-AID 2021), 94% (Kyriazopoulou SAVE-MORE 2021) and 100% (Mariette CORIMUNO-19 Collaborative 2021). The percentage of participants intubated was 11% (Declercq COV-AID 2021), 33% (Derde REMAP-CAP 2021), and none
- Anakinra was compared to placebo in one trial (Kyriazopoulou SAVE-MORE 2021), and compared to standard care in three trials (Declercq COV-AID 2021; Derde REMAP-CAP 2021; Mariette CORIMUNO-19 Collaborative 2021).
- In the four trials reporting on anakinra, three trials reported on the administration of remdesivir at baseline (Declercq COV-AID 2021; Derde REMAP-CAP 2021; Kyriazopoulou SAVE-MORE 2021). In all trials, the use of remdesivir was balanced, i.e. 73% vs 70% (Kyriazopoulou SAVE-MORE 2021), 30% vs 26% (Derde REMAP-CAP 2021), 7% vs 4% (Declercq COV-AID 2021).

Qualität der Studien:

- Low to some concerns

Studienergebnisse:

Outcomes	Anticipated absolute effects* (95% CI) Risk with standard care/ placebo	Risk with anakinra	Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)
Clinical improvement D28	737 per 1000	796 per 1000 (715 to 884)	**RR 1.08** (0.97 to 1.20)	837 (3 RCTs)[a]	⊕⊕⊕⊖ **moderate**[b]
Clinical improvement D60 or above	847 per 1000	788 per 1000 (661 to 949)	**RR 0.93** (0.78 to 1.12)	115 (1 RCT)[c]	⊕⊖⊖⊖ **very low**[d,e]
WHO Clinical Progression Score of level 7 or above D28	167 per 1000	112 per 1000 (60 to 204)	**RR 0.67** (0.36 to 1.22)	722 (2 RCTs)[f]	⊕⊕⊖⊖ **low**[g,h]
WHO Clinical Progression Score of level 7 or above D60 or above	103 per 1000	56 per 1000 (31 to 99)	**RR 0.54** (0.30 to 0.96)	606 (1 RCT)[i]	⊕⊕⊖⊖ **low**[e,j]
All-cause mortality D28	104 per 1000	71 per 1000 (35 to 144)	**RR 0.69** (0.34 to 1.39)	722 (2 RCTs)[f]	⊕⊕⊖⊖ **low**[k]
All-cause mortality D60 or above	262 per 1000	270 per 1000 (178 to 408)	**RR 1.03** (0.68 to 1.56)	1633 (4 RCTs)[l]	⊕⊖⊖⊖ **very low**[h,m,n]
Adverse events	713 per 1000	727 per 1000 (670 to 792)	**RR 1.02** (0.94 to 1.11)	722 (2 RCTs)[f]	⊕⊕⊕⊖ **moderate**[b,o]
Serious adverse events	247 per 1000	235 per 1000 (143 to 385)	**RR 0.95** (0.58 to 1.56)	722 (2 RCTs)[f]	⊕⊕⊖⊖ **low**[h,o,p]
Time to clinical improvement Follow-up: 28 to 90 days	762 per 1000[q]	784 per 1000 (729 to 836)	**HR 1.07** (0.91 to 1.26)	1633 (4 RCTs)[l]	⊕⊕⊖⊖ **low**[r,s]
Time to WHO Clinical Progression Score of level 7 or above Follow-up: 28 to 90 days	187 per 1000[t]	133 per 1000 (95 to 186)	**HR 0.69** (0.48 to 0.99)	722 (2 RCTs)[f]	⊕⊕⊖⊖ **low**[e]
Time to death Follow-up: 28 to 90 days	267 per 1000[u]	220 per 1000 (167 to 285)	**HR 0.80** (0.59 to 1.08)	1518 (3 RCTs)[v]	⊕⊕⊖⊖ **low**[w]

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **HR:** hazard Ratio; **RR:** risk ratio; **WHO:** World Health Organization

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate;: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

Explanations

[a] Declercq COV-AID 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021
[b] Imprecision downgraded by one level due to low number of participants.
[c] Declercq COV-AID 2021
[d] Indirectness downgraded by one level: despite a multicentre design this is a single study from a single country, therefore results in this population might not be generalisable to other settings.
[e] Imprecision downgraded by two levels due to low number of participants and events.
[f] Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021
[g] Inconsistency downgraded by one level: $I^2 = 60.0\%$.
[h] Imprecision downgraded by one level due to wide confidence interval consistent with the possibility for benefit and the possibility for harm, and low number of participants and events. This outcome was not downgraded an additional level for imprecision because it was downgraded one level for inconsistency, which is related to and would have contributed to the severity of the imprecision.
[i] Kyriazopoulou SAVE-MORE 2021
[j] Multicentre study conducted across several countries, therefore not downgraded for indirectness.
[k] Imprecision downgraded by two levels due to wide confidence interval consistent with the possibility for benefit and the possibility for harm, and low number of participants and events.
[l] Declercq COV-AID 2021; Derde REMAP-CAP 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021
[m] Risk of bias downgraded by one level: some concerns regarding deviation from intended interventions and missing data.
[n] Inconsistency downgraded by one level: $I^2 = 63.2\%$.
[o] One additional study was identified that measured this outcome, but no results were reported.
[p] Inconsistency downgraded by one level: $I^2 = 68.2\%$.
[q] Control group risk calculated from Declercq COV-AID 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021.
[r] Risk of bias downgraded by one level: some concerns regarding deviation from intended interventions, missing data and outcome measurement.
[s] Imprecision downgraded by one level due to a wide confidence interval consistent with the possibility for benefit and the possibility for no effect.
[t] Control group risk calculated from Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021.
[u] Control risk calculated from Derde REMAP-CAP 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021.
[v] Derde REMAP-CAP 2021; Kyriazopoulou SAVE-MORE 2021; Mariette CORIMUNO-19 Collaborative 2021

Anmerkung/Fazit der Autoren

Our results suggest that anakinra and canakinumab probably result in little or no increase in clinical improvement D28. For all other critical effectiveness outcomes, evidence was of low or very low certainty. Regarding critical safety outcomes, anakinra and canakinumab probably result in little or no increase in adverse events. Evidence for serious adverse events was of low certainty.

The evidence available is not complete. We have identified 16 more registered RCTs evaluating IL-1 blocking agents with no results available, including four completed and four terminated trials. Access to these results is expected and will allow us to update our data.

Kreuzberger et al., 2021 [19].

SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19.

Fragestellung

To assess the effectiveness and safety of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2)-neutralising monoclonal antibodies (mAbs) for treating patients with COVID-19 compared to an active comparator, placebo, or no intervention. To maintain the currency of the evidence, we will use a living systematic review approach.

A secondary objective is to track newly developed SARS-CoV-2-targeting mAbs from first tests in humans onwards.

Methodik

<u>Population:</u>

- confirmed diagnosis of COVID-19 (virus antigens or RNA detected)

<u>Intervention:</u>

- SARS-CoV-2-neutralising mAbs.
- 'Antibody cocktails' that include SARS-CoV-2-neutralising mAbs

- We excluded SARS-CoV-2-neutralising mAbs used for prevention of COVID-19 and we excluded mAbs that are not specifically designed to treat COVID-19 (such as nivolumab, tocilizumab, canakinumab, etc.).

➢ Aufgrund des Zulassungsstatus werden nur die Ergebnisse von Casirivimab/Imdevimab, Regdanvimab und Sotrovimab dargestellt

Komparator:

- drug treatments (including, but not limited to hydroxychloroquine, remdesivir), standard or hyperimmune immunoglobulin, convalescent plasma, or others.
- no treatment or placebo.

Endpunkte:

- All-cause mortality at up to 30 days
- All-cause mortality at up to 60 days
- Clinical progression, improvement of symptoms, or development of severe symptoms according to the WHO scale
- Quality of life, including fatigue, assessed with standardized scales, for example, WHOQOL-100, at up to seven days; up to 30 days, and longest follow-up available
- Admission to hospital or death for non-hospitalised and hospital discharge and alive for hospitalised participants
- (Serious) adverse events
- Length of hospital stay (for those admitted to hospital)
- Admission to intensive care unit (ICU)
- Length of ICU stay
- Viral clearance, assessed with reverse transcription-polymerase chain reaction (RT-PCR) test for SARS-CoV-2 at baseline, up to three, seven, and 15 days
- Time to sustained recovery (for hospitalised participants)
- Neurologic dysfunction (for hospitalised participants)
- Thromboembolic events
- Renal failure

Recherche/Suchzeitraum:

- We restricted the database search to records added since 1 January 2020, as the first studies on COVID-19 were registered on 23 January 2020 (Zhu 2020). We searched the following databases up to 17 June 2021: MEDLINE, Embase, Cochrane COVID-19 Study Register, PubMed, Epistemonikos COVID-19 L*VE Platform, World Health Organization COVID-19 Global literature on coronavirus disease
- The search for platform trials was conducted every two months (from November 2020 to July 2021).

Qualitätsbewertung der Studien:

- Risk of Bias 2.0 (RoB 2) tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 6 RCTs (in 28 records) are included in this review, of which three are published as preprint only and one as journal publication with additional data from two preprints.
- 31 RCTs (in 39 records) on 18 different mAbs or mAb combinations are currently ongoing.
- 2 platform trials (29 attached records) are included (already identified by mAbs-specific search), one of these has added new treatment arms and is thus also listed as an ongoing study;
- 4 platform trials (13 records) with at least one mAb as an experimental treatment are ongoing (already identified by mAbs-specific search);
- 30 platform trials (69 records) that may potentially add a mAb during the course of the study are ongoing.
- All six included RCTs are still active or ongoing due to different reasons.
- We included six RCTs (ACTIV-3; BLAZE-1 (phase 2); BLAZE-1 (phase 3); COMET-ICE; Eom 2021; RECOVERY; Weinreich (phase 1/2); Weinreich (phase 3)). These included 17,495 randomised participants: 486 participants were assigned to receive varying doses of bamlanivimab (0.7 g, 2.8 g, 7.0 g, ACTIV-3; BLAZE-1 (phase 2)), 632 participants were assigned to receive combination therapy of bamlanivimab and etesevimab (2.8 g each; BLAZE-1 (phase 2); BLAZE-1 (phase 3)), 3600 participants were assigned to receive a combination of casirivimab and imdevimab at different doses (1.2 g, 2.4 g, 8.0 g; Weinreich (phase 1/2); Weinreich (phase 3)), 430 participants were assigned to receive sotrovimab (COMET-ICE), and 216 participants were assigned to receive regdanvimab (0.04 g/kg or 0.08 mg/kg, Eom 2021). In RECOVERY 4839 participants were allocated to receive a combination of casirivimab and imdevimab (8.0 g).

Charakteristika der Population:

- Four studies included non-hospitalised participants with clinical symptoms of mild disease according to the definition of the WHO Clinical Progression Scale (Figure 1; BLAZE-1 (phase 2); COMET-ICE; Eom 2021; Weinreich (phase 1/2); Weinreich (phase 3)).
- Risk factors for severe COVID-19 progression were present in 60.5% in Weinreich (phase 1/2), 67% in BLAZE-1 (phase 2) and 99.7% in COMET-ICE. In Weinreich (phase 3) all participants had at least one risk factor for severe COVID-19 and in Eom 2021 73.44% had comorbidities at baseline.

Qualität der Studien:

- Casirivimab/imdevimab compared to placebo in nonhospitalised individuals with COVID-19 (asymptomatic or mild disease)
  - We judged the risk of bias for Weinreich (phase 1/2) (preprint), the only study assessing the combination of casirivimab and imdevimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be of low risk of bias across the outcomes grades 3 to 4 adverse events and serious adverse events. For the outcome hospital admission or death we judged the risk of bias to be of some concern because the statistical analysis plan and protocol were not provided with the preprint.
  - Andere outcomes wurden nicht berichtet
  - For Weinreich (phase 3) (preprint), we judged the risk of bias to be high across the outcomes: mortality by day 30, clinical progression/improvement of symptoms, admission to hospital or death, length of hospital stay, admission to ICU, adverse events

(all grades and grades 3 to 4) and serious adverse events, because participants without risk factors were excluded from analysis and it was unclear which participants were included in the analysis set. More participants were missing than the ones not receiving or discontinuing treatment. Furthermore, data for participants who received casirivimab/imdevimab at a dose of 8.0 g were not reported on all relevant outcomes.
    - Andere outcomes wurden nicht berichtet
    - Due to the high risk of bias, reported outcomes were not included in the analysis but reported narratively instead.
- Casirivimab/imdevimab compared to placebo in hospitalized individuals with COVID-19 (moderate and severe disease)
    - We judged the risk of bias for RECOVERY, the only study assessing casirivimab/imdevimab in hospitalised individuals to be high across the outcomes: all-cause mortality up to 30 days, development of severe symptoms according to WHO scale, hospital discharge alive by day 30, thromboembolic events and renal dysfunction (need for dialysis), because of the open-label design of the study control group participants may have received concomitant treatment more quickly.
    - Andere outcomes wurden nicht berichtet
- Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)
    - We judged the risk of bias for COMET-ICE, the only study assessing sotrovimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be some concerns across the outcomes: all-cause mortality up to 30 days, development of severe symptoms according to WHO scale, admission to hospital or death, admission to ICU and for safety outcomes (adverse events (all grades and grades 3 to 4), and serious adverse events, because the trial was stopped preliminary and protocol or statistical analysis plan were not available.
    - Andere outcomes wurden nicht berichtet
- Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)
    - We judged the risk of bias for Eom 2021, the only study assessing regdanvimab in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease) to be low across the outcomes: mortality up to 30 days, development of severe symptoms, admission to hospital or death, admission to ICU and viral clearance at day 15, and safety outcomes (adverse events all grades, adverse events grades 3 to 4 and serious adverse events.
    - Andere outcomes wurden nicht berichtet

Studienergebnisse:

Summary of findings 3. Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Casirivimab/imdevimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic or mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatients **Intervention**: casirivimab/imdevimab **Comparison**: placebo

Outcomes	Dose	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with casirivimab/imdevimab				
Mortality by day 30	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Mortality by day 60	not reported	-		-	-	-	We did not identify any study reporting this outcome.
Clinical progression: requirement of IMV (WHO 7, 8 or 9), 1.2g	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Quality of life	not measured	-		-	-	-	We did not identify any study reporting this outcome.
Admission to hospital or death	1.2g	-		-	-	-	
	2.4g	22 per 1000	**9 per 1000** (2 to 47)	**RR 0.43** (0.08 to 2.19)	446 (1 RCT)	⊕⊕⊖⊖ Low[a]	Casirivimab/imdevimab at 2.4 g or 8.0 g may reduce the occurrence of hospital admissions or death at day 30.
	8.0g	22 per 1000	**5 per 1000** (0 to 39)	**RR 0.21** (0.02 to 1.79)	450 (1 RCT)		
Adverse events: grade 3-4	1.2g	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
	2.4g	15 per 1000	**12 per 1000** (3 to 51)	**RR 0.76** (0.17 to 3.37)	520 (1 RCT)	⊕⊕⊖⊖ Low[a]	There were too few who experienced am event to determine whether any dose of casirivimab/imdevimab made a difference
	8.0g	15 per 1000	**8 per 1000** (1 to 42)	**RR 0.50** (0.09 to 2.73)	522 (1 RCT)		
Adverse events: all grades	not reported	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
Serious adverse events	1.2g	-		-	-	-	Only one study which was excluded from analysis reported results on this outcome.
	2.4g	23 per 1000	**16 per 1000** (4 to 54)	**RR 0.68** (0.19 to 2.37)	520 (1 RCT)	⊕⊕⊖⊖ Low[a]	There were too few who experienced am event to determine whether any dose of casirivimab/imdevimab made a difference.
	8.0g	23 per 1000	**8 per 1000** (2 to 38)	**RR 0.34** (0.07 to 1.65)	522 (1 RCT)		

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels due to very serious imprecision; low sample size and low number of events

Summary of findings 4. Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Sotrovimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatients **Intervention**: sotrovimab **Comparison**: placebo

Outcome	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants** (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with placebo	Risk with sotrovimab				
Mortality by day 30	3 per 1000	**1 per 1000** (0 to 28)	**RR 0.33** (0.01 to 8.18)	583 (1 RCT)	⊕⊖⊖⊖ Low[a]	There were too few who experienced mortality to determine whether sotrovimab made a difference.
Mortality by day 60	not reported		-	-	-	We did not identify any study reporting this outcome.
Clinical progression: oxygen requirement (≥ 5 WHO scale)	65 per 1000	**7 per 1000** (1 to 29)	**RR 0.11** (0.02 to 0.45)	583 (1 RCT)	⊕⊖⊖⊖ Low[b]	Sotrovimab may reduce the number of participants with any oxygen requirement.
Clinical progression: IMV or death (≥ 7 WHO scale)	10 per 1000	**1 per 1000** (0 to 28)	**RR 0.14** (0.01 to 2.76)	583 (1 RCT)	⊕⊖⊖⊖ Low[a]	There were too few who experienced an event to determine whether sotrovimab made a difference.
Quality of life by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.
Admission to hospital or death by day 30	72 per 1000	**10 per 1000** (3 to 35)	**RR 0.14** (0.04 to 0.48)	583 (1 RCT)	⊕⊖⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of hospital admissions or death.
Adverse events: all grades	194 per 1000	**169 per 1000** (128 to 225)	**RR 0.87** (0.66 to 1.16)	868 (1 RCT)	⊕⊖⊖⊖ Low[b]	Sotrovimab may have little to no effect on the occurrence of all grade adverse events.
Adverse events: grades 3 and 4	62 per 1000	**16 per 1000** (7 to 37)	**RR 0.26** (0.12 to 0.60)	868 (1 RCT)	⊕⊖⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of grade 3-4 adverse events.
Serious adverse events	59 per 1000	**16 per 1000** (7 to 37)	**RR 0.27** (0.12 to 0.63)	868 (1 RCT)	⊕⊖⊖⊖ Low[b]	Sotrovimab may reduce the occurrence of serious adverse events.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**This study included a total of 868 participants. All were 868 participants randmoised were included in the safety set, but only 583 participants were analysed in the efficacy set.

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels for very serious imprecision, because of low sample size, very low number of events and very wide confidence interval
[b] Downgraded two levels for very serious imprecision, because of low sample size and/or low number of events

Summary of findings 5. Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Regdanvimab compared to placebo in non-hospitalised individuals with COVID-19 (asymptomatic and mild disease)

Patient or population: non-hospitalised individuals with COVID-19 (asymptomatic and mild disease) **Setting**: outpatient **Intervention**: regdanvimab **Comparison**: placebo

Outcomes		Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
		Risk with placebo	Risk with regdanvimab				
Mortality by day 30	Regdanvimab 40mg/kg CT-P59 80 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	⊕⊖⊖⊖ Low[a]	No events observed. We are uncertain whether CT-P59 has any impact on mortality at up to day 30.
Mortality by day 60	not reported	-	-	-	-	-	-
Clinical progression: development of severe symptoms (≥ 7 WHO scale, IMV)	40 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	Not estimable	(1 RCT)	⊕⊖⊖⊖ Low[a]	No events observed. We are uncertain whether 40 mg/kg regdanvimab has any impact on IMV requirement or death.
	80 mg/kg	0 per 1000	**0 per 1000** (0 to 0)	**RR 3.00** (0.12 to 72.80)	103 (1 study)	⊕⊖⊖⊖ Low[b]	There were too few who experienced IMV or death to determine whether CT-P59, 80 mg/kg made a difference.
Quality of life by day 30	not measured	-	-	-	-	-	
Admission to hospital or death by day 30	40 mg/kg	87 per 1000	**39 per 1000** (12 to 124)	**RR 0.45** (0.14 to 1.42)	204 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab, 40 mg/kg or 80 mg/kg may decrease hospital admission or death by day 30.
	80 mg/kg	87 per 1000	**49 per 1000** (17 to 140)	**RR 0.56** (0.19 to 1.60)	206 (1 RCT)		
Adverse events: all grades	40 mg/kg	309 per 1000	**297 per 1000** (198 to 442)	**RR 0.96** (0.64 to 1.43)	215 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab 40 mg/kg may have little to no effect on all grade adverse events.
	80 mg/kg	309 per 1000	**244 per 1000** (161 to 377)	**RR 0.79** (0.52 to 1.22)	220 (1 RCT)		Regdanvimab 80 mg/kg may reduce the occurrence of all grade adverse events.
Adverse events: grades 3 and 4	40 mg/kg	18 per 1000	**48 per 1000** (9 to 239)	**RR 2.62** (0.52 to 13.12)	215 (1 RCT)	⊕⊖⊖⊖ Low[b]	Regdanvimab 40 mg/kg or 80 mg/kg may increase the occurrence of grade 3 adverse events.
	80 mg/kg	18 per 1000	**36 per 1000** (7 to 195)	**RR 2.00** (0.37 to 10.70)	220 (1 RCT)		
Serious adverse events by day 30	not reported	0 per 1000	0 per 1000 (0 to 0)	not estimable	(1 RCT)	⊕⊖⊖⊖ Low[b]	We are uncertain whether regdanvimab, 40 mg/kg or 80 mg/kg has an effect on serious adverse events.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded two levels for very serious imprecision, because no events were observed, the sample size small and the effect not estimable
[b] Downgraded two levels for very serious imprecision, because few event(s) were observed and/or the sample size was small.

Summary of findings 7. Casirivimab/Imdevimab compared to usual care alone in hospitalised individuals with COVID-19 (moderate to severe disease)

Casirivimab/imdevimab compared to usual care in hospitalised individuals with COVID-19 (moderate to severe disease)

Patient or population: hospitalised individuals with COVID-19 (moderate to severe disease) **Setting**: inpatient **Intervention**: casirivimab/imdevimab **Comparison**: usual care alone

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty in the evidence (GRADE)	Comments
	Risk with usual care alone	Risk with casirivimab/imdevimab				
Mortality by day 30	236 per 1000	**221 per 1000** (205 to 241)	**RR 0.94** (0.87 to 1.02)	9785 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on mortality by day 30 in the overall cohort of hospitalised participants.
Mortality by day 60	not reported			-	-	We did not identify any study reporting this outcome.
Clinical progression: need for IMV or death (WHO ≥ 7)	248 per 1000	**238 per 1000** (223 to 258)	**RR 0.96** (0.90 to 1.04)	9198 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on IMV requirement or death by day 30 in the overall cohort of hospitalised participants.
Quality of life	not measured		-	-	-	We did not identify any study reporting this outcome.
Hospital discharge alive by day 30	690 per 1000	**697 per 1000** (676 to 718)	**RR 1.01** (0.98 to 1.04)	9785 (1 RCT)	⊕⊕⊕⊖ Moderate[a]	Casirivimab/imdevimab 8.0 g has probably little to no effect on discharge from hospital alive by day 30 in the overall cohort of hospitalised participants.
Adverse events: grades 3 and 4 by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.
Serious adverse events by day 30	not reported		-	-	-	We did not identify any study reporting this outcome.

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio; **RCT:** randomised controlled trial

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.

Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is the possibility that it is substantially different.

Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.

Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

[a] Downgraded one level due to serious risk of bias, the study was not blinded. Currently, there is no clearly defined standard of care for COVID-19, therefore, a lack of blinding can have resulted in differential treatments/timings of treatment between arms.

Anmerkung/Fazit der Autoren

Non-hospitalised individuals

Casirivimab/imdevimab may reduce hospital admissions, however, the confidence interval includes both benefits and harms. For the outcomes grade 3 to 4 adverse events and serious adverse events, there were too few events to allow a judgment. No other outcomes were reported in part 1/2 of the study. Evidence should be considered uncertain due to very serious imprecision.

Sotrovimab may reduce the number of participants with oxygen requirement, hospitalisations or death, the number of hospital admissions or death, and the occurrence of grades 3 to 4 and serious adverse events compared to placebo, although the confidence intervals include both benefit and harms. Events for the outcomes mortality and invasive mechanical ventilation (IMV) requirement or death were too rare to allow a judgment on the effect. Data for this

comparison should be interpreted with caution as they originate from one small study with low number of events and wide confidence intervals.

Evidence suggests that **regdanvimab** at either 40 mg or 80 mg/ kg may reduce hospital admissions, and the 80 mg/kg dose may reduce adverse events when compared with placebo, although the confidence interval includes both benefits and harms. In contrast, regdanvimab may increase grade 3 adverse events, however, the confidence intervals include both benefit and harm. It may have little to no effect on viral clearance at day 15. We could not assess mortality, IMV requirement or death, serious adverse events, and admission to: intensive care unit (ICU), as no or few events took place. Due to the small sample size and low number of events, any evidence has to be interpreted with caution.

Hospitalised individuals

Evidence for **casirivimab/imdevimab** suggests that the treatment at a dose of 8.0 g may have little to no effect on all-cause mortality, clinical progression to IMV or death, hospital discharge alive, thrombotic events, and renal replacement therapy requirement compared with usual care alone in the complete randomized cohort. We have moderate certainty in the evidence due to high risk of bias. In line with the subgroups from ACTIV-3, when looked at seronegative participants at baseline only, the study authors found an effect, while no effect was found for participants who already seroconverted or with unknown status.

Ghosn L et al., 2021 [13].

Interleukin-6 blocking agents for treating COVID-19: a living systematic review.

Fragestellung

To assess the effects of IL-6 blocking agents compared with standard care alone or with placebo on effectiveness and safety outcomes in patients with COVID-19.

This review is part of a larger project: the COVID-NMA project (Boutron 2020a). The COVID-NMA project provides decisionmakers with a complete, high-quality and up-to-date mapping and synthesis of evidence on interventions for preventing and treating COVID-19. We developed a master protocol on the effect of all interventions for preventing and treating COVID-19 (Boutron 2020b). Our results are made available and updated weekly on the COVID-NMA platform at covid-nma.com.

This living review focuses on SARS-CoV-2 and does not consider studies evaluating treatment with IL-6 blocking agents for other coronavirus infections affecting humans.

Methodik

Population:

- children or adults with suspected, probable, or confirmed COVID-19

Intervention:

- Tocilizumab (humanised monoclonal antibody against the IL-6 receptor)
- Sarilumab (human monoclonal antibody against the IL-6 receptor)
- Clazakizumab (humanised rabbit monoclonal antibody against IL-6)
- Olokizumab (humanised monoclonal antibody against IL-6)
- Siltuximab (chimeric monoclonal antibody against IL-6)
- Levilimab (human monoclonal antibody against the IL-6 receptor)

➢ Aufgrund des Zulassungsstatus werden nur die Ergebnisse von Tocilizumab dargestellt

Komparator:

- standard care alone or with placebo;
- standard of care as defined by trialists.

Endpunkte:

- Clinical improvement (D28/ ≥ D60) defined as a hospital discharge or improvement on the scale used by trialists to evaluate clinical progression and recovery.
- WHO Clinical Progression Score of level 7 or above (i.e. mechanical ventilation +/- additional organ support (extracorporeal membrane oxygenation (ECMO), vasopressors or dialysis) or death (D28/ ≥ D60).
- All-cause mortality (D28/ ≥ D60).
- (Serious) adverse events (S)(AEs)
- Time to clinical improvement
- Time to WHO Clinical Progression Score of level 7 or above
- Time to death

Recherche/Suchzeitraum:

- We conducted an evaluation of two secondary sources the L-OVE platform and the Cochrane COVID-19 Study Register
- The last search date was 26 February 2021.

Qualitätsbewertung der Studien:

- RoB 2

Ergebnisse

Anzahl eingeschlossener Studien:

- Ten RCTs (seven published in peer-reviewed journals and three reported as preprints) evaluating IL-6 blocking agents were included in this review. Nine RCTs evaluated tocilizumab including one platform trial evaluating tocilizumab and sarilumab, and one three-arm trial evaluated sarilumab.
- Seven trials evaluated tocilizumab 8 mg/kg by infusion for one day (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021); the dose was adapted to patients' weight according to an algorithm in one trial (Horby RECOVERY 2021), and one evaluated a lower dose of 400 mg by infusion for one day (Wang 2020). A second infusion was allowed in six trials (Gordon REMAPCAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Rosas COVACTA 2021; Salvarani 2020; Wang 2020).
- The use of steroids at baseline was reported in eight trials (Gordon REMAP-CAP 2021; Hermine CORIMUNO-19 2020; Horby RECOVERY 2021; Lescure 2021; Rosas COVACTA 2021; Salama EMPACTA 2020; Salvarani 2020; Stone 2020; Veiga TOCIBRAS 2021). Three trials reported that more participants received steroids in the control group (Hermine CORIMUNO-19 2020; Rosas COVACTA 2021; Salama EMPACTA 2020). There was some cross-over planned in the protocol in one trial (Salvarani 2020), with 22% of participants in the control arm receiving the experimental treatment.

Charakteristika der Population:

- We included a total of 6896 participants (10 RCTs) in the analysis of this review. Overall, 6428 participants (nine RCTs) were included in the analysis comparing tocilizumab with control
- The mean age range varied from 56 to 65 years; 4572/6896 (66.3%) were men.
- Participants had mild to critical disease in one RCT (N = 452) (Rosas COVACTA 2021), mild to severe diseases in two RCTs (N = 625) (Salama EMPACTA 2020; Stone 2020), moderate to severe disease in two RCTs (N = 196) (Hermine CORIMUNO-19 2020; Wang 2020), moderate to critical disease in three RCTs (N = 4665) (Horby RECOVERY 2021; Lescure 2021; Veiga TOCIBRAS 2021), severe disease in one RCT (N = 158) (Salvarani 2020), and severe to critical disease in one RCT (N = 826) (Gordon REMAP-CAP 2021). Inflammation makers varied but was high in most trials.
- The percentage of participants on oxygen at baseline but not intubated was 56% (Rosas COVACTA 2021), 71% (Gordon REMAPCAP 2021), 84% (Stone 2020), 84% (Veiga TOCIBRAS 2021), 86% (Horby RECOVERY 2021), 87% (Lescure 2021), 88% (Salama EMPACTA 2020), 100% (Hermine CORIMUNO-19 2020; Wang 2020). One trial did not provide this information (Salvarani 2020). Five trials reported the percentage of patients that were intubated at baseline: 12% (Lescure 2021), 14% (Horby RECOVERY 2021), 16% (Veiga TOCIBRAS 2021), 29% (Gordon REMAP-CAP 2021), and 37% (Rosas COVACTA 2021). In the other trials, no patient was intubated at baseline (a single patient intubated at baseline in the control group in Stone 2020).

Qualität der Studien:

- Low bis some concerns. Wang hatte in allen Endpunkten, für die die Studie ausgewertet werden konnte ein hohes Verzerrungsrisiko

Studienergebnisse:

Summary of findings 1. Tocilizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Tocilizumab compared to standard care/placebo for mild/moderate/severe/critical COVID-19

Patient or population: participants with mild/moderate/severe/critical COVID-19

Settings: Brazil, China, France, Italy, UK, USA

Intervention: tocilizumab

Comparison: standard care/placebo

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with standard care/ placebo	Risk with tocilizumab				
Clinical improvement D28	**515 per 1000**	**545 per 1000** (515 to 581)	**RR 1.06** (1.00 to 1.13)	5585 (7 RCTs)	⊕⊕⊕⊖ **moderate** [1]	Data at D ≥ 60 was not available Clinical improvement was defined variably as an improvement from baseline in > 2 categories on a 7-category ordinal scale (2 studies); a decrease of at least 2 points on an ordinal clinical improvement scale (1 study); or hospital discharge or ready to discharge (7 studies)

WHO progression score (level 7 or above) D28	**262 per 1000**	**260 per 1000** (147 to 457)	**RR 0.99** (0.56 to 1.74)	712 (3 RCTs)	⊕⊕⊖⊖ **low** [2,3]	Data at D ≥ 60 was not available
All-cause mortality D28	**291 per 1000**	**259 per 1000** (239 to 283)	**RR 0.89** (0.82 to 0.97)	6363 (8 RCTs	⊕⊕⊕⊕ **high** [4]	
All-cause mortality D60	**133 per 1000**	**114 per 1000** (70 to 186)	**RR 0.86** (0.53 to 1.40)	519 (2 RCTs)	⊕⊕⊖⊖ **low** [5,6]	
Adverse events	**457 per 1000**	**562 per 1000** (397 to 786)	**RR 1.23** (0.87 to 1.72)	1534 (7 RCTs)	⊕⊖⊖⊖ **very low** [7,8,9]	
Serious adverse events	**149 per 1000**	**132 per 1000** (111 to 157)	**RR 0.89** (0.75 to 1.06)	2312 (8 RCTs)	⊕⊕⊕⊖ **moderate** [7]	
Time to clinical improvement 28 to 90 days follow-up	**High** **889 per 1000**	**933 per 1000** (917 to 957	**HR 1.23** (1.08 to 1.39)	2118 (6 RCTs)	⊕⊕⊕⊖ **moderate** [1, 13]	
Time to WHO progression score (level 7 and above) 28 to 90 days follow-up	**Low** **123 per 1000**	**78 per 1000** (54 to 113)	**HR 0.62** (0.42 to 0.91)	762 (3 RCTs)	⊕⊕⊕⊖ **moderate** [10, 11, 13]	
Time to death follow-up 28 to 90 days	**Low** **37 per 1000**	**24 per 1000** (19 to 31)	**HR 0.65** (0.51 to 0.83)	1152 (3 RCTs)	⊕⊕⊖⊖ **low** [2, 12, 13]	

***The risk in the intervention group** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk Ratio; **HR**: Hazard Ratio: **WHO**: World Health Organization

GRADE Working Group grades of evidence

High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect.

[1] Risk of bias downgraded by 1 level: some concerns due to deviation from intended interventions and outcome measurement
[2] Risk of bias downgraded by 1 level: some concerns due to deviations from intended interventions
[3] Imprecision downgraded by 1 level: due to wide confidence interval consistent with the possibility for benefit and the possibility for harm
[4] Despite some concerns due to deviation from intended interventions, risk of bias was not downgraded because the studies at risk contributed < 20% weight to the effect estimate.
[5] Despite some concerns due to deviation from intended intervention in 1 study, risk of bias was not downgraded because this study contributed only 30% weight to the effect estimate.

[6] Imprecision downgraded by 2 levels: due to low number of events and a wide confidence interval consistent with the possibility for benefit and the possibility for harm
[7] Risk of bias downgraded by 1 level: some concerns regarding randomisation, deviations from intended interventions, outcome measurement and selection of reported result
[8] Inconsistency downgraded by 1 level: $I^2 = 86.4\%$
[9] Imprecision downgraded by 1 level: due to a wide confidence interval consistent with the possibility for no effect and the possibility for harm
[10] Despite some concerns due to deviation from intended intervention in 2 studies, risk of bias was not downgraded.
[11] Imprecision downgraded by 1 level: due to low number of events and a wide confidence interval consistent with the possibility for benefit and the possibility for little or no effect
[12] Imprecision downgraded by 1 level: due to low number of events and participants
[13] Control group risk at 28 days from Stone 2020

Anmerkung/Fazit der Autoren

Our results suggest that on average tocilizumab reduces all-cause mortality at D28 compared to standard care alone or placebo. Results of important outcomes (time to clinical improvement, time to WHO progression score level 7 or above and time to death) were consistent with a beneficial effect of tocilizumab. Nevertheless, tocilizumab probably results in little or no increase in the outcome clinical improvement defined as hospital discharge or improvement on the scale used by trialists at Day D28. The discrepancy in these results could

be related to the large variation in the information size across the outcomes. The beneficial effect of tocilizumab has been debated because of the important discrepancies in trial results. Several explanations for these discrepancies were discussed, particularly differences in cointerventions, particularly steroid, timing of treatment, severity of the disease, participants pattern of immune reaction (McCreary 2021). With the data available, we were not able to explore heterogeneity. Individual patient data meta-analyses are needed to be able to identify which patients are more likely to benefit from this treatment.

Regarding safety outcomes, tocilizumab probably slightly reduces serious adverse events. Evidence for its effect on all other critical outcomes was of low or very low certainty.

Kommentare zum Review

SR mit vergleichbarer Methodik und vergleichbaren Ergebnissen (vor allem im Hinblick auf Vorteil bei OS)

- Zhang J et al., 2022 [42]. Effectiveness of tocilizumab in the treatment of hospitalized adults COVID-19: A systematic review and meta-analysis.
  - Es wurde zusätzlich incidence of mechanical ventilation ausgewertet, wobei sich ein Vorteil für Tocilizumab zeigte (RR 0,79 [0,71-0,89]
  - Es wurde ebenfalls ein statistisch signifikanter Vorteil bei der Einweisung in ICU gezeigt
- Avni T et al., 2021 [4]. Tocilizumab in the treatment of COVID-19-a meta-analysis
  - Zusätzlich statistisch signifikanter Vorteil für incidence of mechanical ventilation und Einweisung in ICU
- Conti V et al., 2021 [9]. Effect of Tocilizumab in Reducing the Mortality Rate in COVID-19 Patients: A Systematic Review with Meta-Analysis
  - Mortalität insgesamt erfasst: in RCTs kein statistisch signifikanter Unterschied.
- Malgie J et al., 2021 [23]. Decreased mortality and increased side effects in COVID-19 patients treated with IL-6 receptor antagonists: systematic review and meta-analysis
- Selvaraj V et al., 2021 [28]. Tocilizumab in Hospitalized Patients with COVID-19: A Meta Analysis of Randomized Controlled Trials.
  - Zusätzlich statistisch signifikanter Vorteil für incidence of mechanical ventilation
- Shankar-Hari M et al., 2021 [29]. Association Between Administration of IL-6 Antagonists and Mortality Among Patients Hospitalized for COVID-19: A Meta-analysis.
  - Insgesamt 19 RCT eingeschlossen
  - The summary OR for the association with mortality for tocilizumab (15 trials, 7490 patients, and 1951 deaths) was 1.06 (95% CI, 0.85-1.33) in patients not receiving corticosteroids at randomization and was 0.77 (95% CI, 0.68-0.87) in patients receiving corticosteroids at randomization
  - Zusätzlich statistisch signifikanter Vorteil für incidence of mechanical ventilation
- Vela D et al., 2021 [37]. Efficacy and safety of tocilizumab versus standard care/placebo in patients with COVID-19; a systematic review and meta-analysis of randomized clinical trials.
  - 10 RCT eingeschlossen
  - Zusätzlich statistisch signifikanter Vorteil für incidence of mechanical ventilation
  - concomitant corticosteroid use was associated with a statistically significantly lower RR for death. This benefit was not observed in patients with no corticosteroid use.
- Kyriakopoulos C et al., 2021 [20]. Tocilizumab administration for the treatment of hospitalized patients with COVID-19: A systematic review and meta-analysis.

SR, in denen kein OS Vorteil gezeigt wurde

- Lin WT et al., 2021 [22]. The effect of tocilizumab on COVID-19 patient mortality: A systematic review and meta-analysis of randomized controlled trials.
  - Es wurden die gleichen Studien eingeschlossen wie bei Ghosn et al. Für die 28 Tage OS Rate wurde statt des RR das OR berechnet.
- Snow TAC et al., 2021 [32]. Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials.
  - Es wurden die gleichen Studien eingeschlossen wie bei Ghosn et al. Für die 28 Tage OS Rate wurde statt des RR das OR berechnet.
- Tleyjeh IM et al., 2021 [35]. Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis, first update.
  - Es wurde eine Studie weniger eingeschlossen als bei Ghosn et al. Statistisch signifikante Vorteile für incidence of mechanical ventilation und 28-30 days composite of poor outcome
- Kow CS et al., 2021 [18]. The effect of tocilizumab on mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials.
  - RECOVERY nicht eingeschlossen
- Gupta S et al., 2022 [14]. Tocilizumab in patients hospitalized with COVID-19 pneumonia: systematic review and meta-analysis of randomized controlled trials.
  - Nur Patient*innen mit Pneumonie
  - 6 RTC eingeschlossen. Statistisch signifikanter Vorteil bei mechanical ventilation/death at 28 days
- Chen et al., 2021 [8]. Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19).
  - Alter SR, nur 3 RCT enthalten
- Juul S et al., 2021 [16]. Interventions for treatment of COVID-19: Second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project)
  - Älterer SR, nur 6 RCT enthalten

3.2 Systematische Reviews

Tu J et al., 2022 [36].

Effects of different corticosteroid therapy on severe COVID-19 patients: a meta-analysis of randomized controlled trials.

Fragestellung

Our meta-analysis aimed to evaluate the safety and efficacy in severe COVID-19 patients to provide a high level of evidence for clinical decisionmaking in treating severe COVID-19 patients

Methodik

Population:

- age>18 years

- hospitalized patients diagnosed with COVID-19

Intervention:

- corticosteroids

Komparator:

- k.A.

Endpunkte:

- The primary outcomes of this study included mortality and adverse events. The secondary outcomes included the need for invasive mechanical ventilation (for patients not intubated at inclusion) and secondary infections.

Recherche/Suchzeitraum:

- An extensive search was conducted from December 2019 to 15 July 2021, in PubMed, EMBASE, the Cochrane Library, China National Knowledge Infrastructure (CNKI), and Wan Fang Data

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 10 articles were included

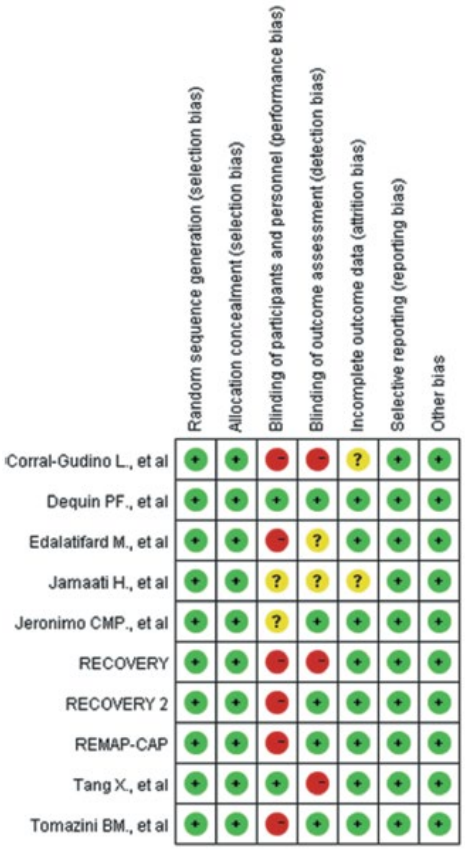
Charakteristika der Population:

Table 1. Characteristics of included randomized clinical trials.

Study	Country	Patients, total n	Male sex n(%)	Age, years	Intervention	Control
Corral-Gudino L, et al	Spain	64(35vs 29)	23(66) vs 16(55)	73 (11) vs 66 (12)	MP 40 mg bid for 3 Days and then 20 mg bid for 3 more days	Standard of care
Dequin PF., et al	France	149(76vs 73)	54 (71.1) vs 50 (68.5)	63.1(51.5–70.8) vs 66.3 (53.5–72.7)	"continuous intravenous infusion of hydrocortisone at an initial dose of 200 mg/duntil 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"	Placebo (saline)
Edalatifard M., et al	Iranian	62(34 vs 28)	24 (70.6%) vs 15 (53 · 5%)	55.8 (16.35) vs 61.7 (16.62)	Standard care with methylprednisolone pulse (intravenous injection, 250 mg/day for 3 days)	Standard care alone
Jamaati H, et al	Iran	50(25 vs 25)	18 (72%) vs 18 (72%)	62(14.07) vs 62 (10.37)	Intravenous dexamethasone at a dose of 20 mg/day from day 1–5 and then at 10 mg/day from day 6–10	Not receive dexamethasone treatment
Jeronimo CMP., et al	Brazil	393(194 vs 199)	126 (64.9) vs 128 (64.3)	54(15) vs 57 (15)	Intravenous sodium succinate Methylprednisolone (0.5 mg/kg) twice daily for 5 days	Placebo (saline solution) twice daily for 5 days
RECOVERY	United Kingdom	6425 (2104 vs 4321)	1338 (64) vs 2749 (64)	66.9(15.4) vs 65.8(15)	The usual standard of care plus oral or intravenous dexamethasone (at a dose of 6 mg once daily) for up to 10 days (or until hospital discharge if sooner)	The usual standard of care alone

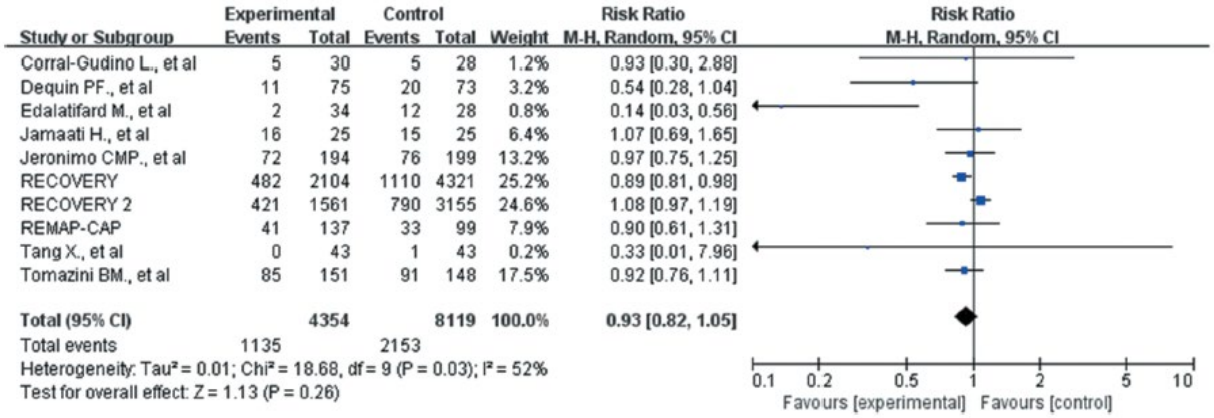
RECOVERY2	United Kingdom	4716 (1561 vs 3155)	960(61.5) vs 1974 (62.6)	65.2(15.2) vs 65.4 (15.4)	Patients received hydroxychloroquine sulfate in a loading dose of four tablets (total dose, 800 mg) at baseline and at 6 hours, which was followed by two tablets (total dose, 400 mg) starting at 12 hours after the initial dose and then every 12 hours for the next 9 days or until discharge	Usual care
REMAP-CAP	Australia, Canada et al	238(137 vs 101)	98 (71.5) vs 72 (71.3)	60.4 (11.6) vs 59.9 (14.6)	A fixed dose of intravenous hydrocortisone, 50 mg, every 6 hours for 7 days.	No hydrocortisone
Tang X, et al	China	86(43 vs 43)	21 (48.8) vs 20 (46.5)	57(13.33) vs 55(20)	1 mg/kg per day of methylprednisolone (produced by Pfizer Manufacturing Belgium NV) dissolved in 100 mL 0.9% normal saline was administered intravenously for 7 days	100 mL 0.9% normal saline
Tomazini BM., et al	Brazil	299(151 vs 148)	90 (59.6) vs 97 (65.6)	60.1 (15.8) vs 62.7 (13.1)	Dexamethasone 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.	Standard care only

Qualität der Studien:



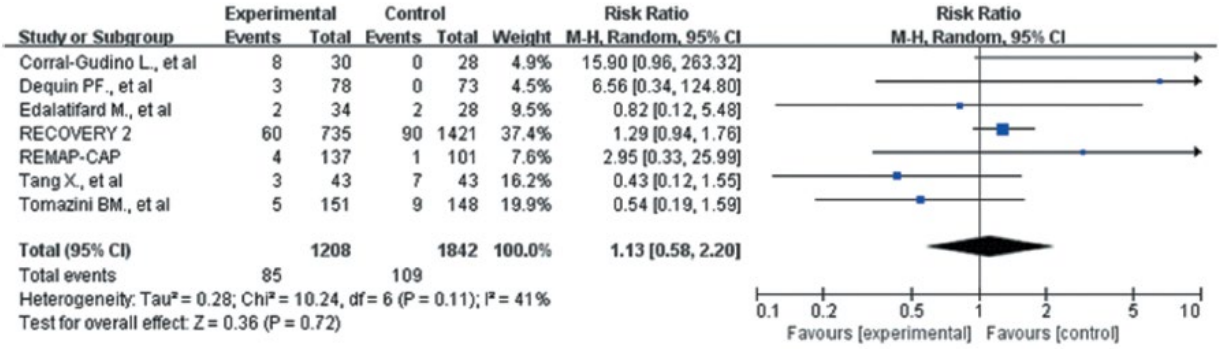
Studienergebnisse:

- All cause mortality

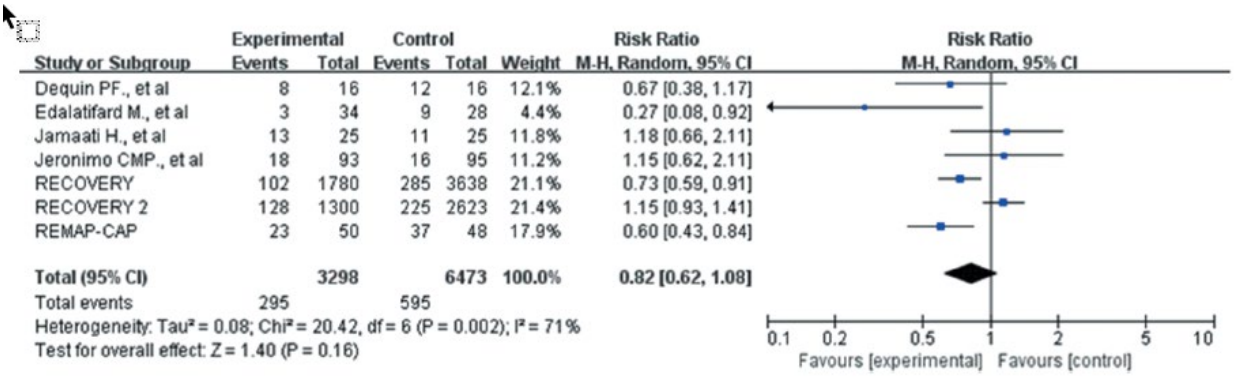


- mortality in the subgroups of patients treated with dexamethasone

- Adverse Events



- invasive mechanical ventilation



Anmerkung/Fazit der Autoren

In this study, a meta-analysis of 10 randomized clinical trials with a total of 12,473 severe COVID-19 patients showed corticosteroids treatment did not significantly reduce mortality. However, the subgroup analysis found the survival benefit was observed in both patients treated with a low dosage of corticosteroids and patients treated with dexamethasone. No increased risk of the need for mechanical ventilation, adverse events, or secondary infections were found. However, due to the great heterogeneity between trials, clear conclusions remain a challenge.

The effect of corticosteroids on patient survival highly depended on the selection of the right dosage and type and in a specific subgroup of patients [27]. Pasin et al. [29] found a reduction in mortality was observed in the subgroup of patients who required mechanical ventilation. It was recommended that severe patients could consider corticosteroids therapy. In our meta-analysis, the survival benefit of corticosteroid therapy was not observed in the subgroup of patients requiring mechanical ventilation.

Subgroup analyses of different dosages and types of corticosteroids were performed in our meta-analysis. The survival benefit was observed in a low dosage of corticosteroids but not in high-dose corticosteroids. Similar to Ma et al.'s findings [27]. 8 studies used low-dose corticosteroids (25–150 mg/d, methylprednisolone) and 2 studies used high-dose corticosteroids (>150 mg/d, methylprednisolone) [30].

The survival benefit was also observed in treatment with dexamethasone. In our study, the main types of corticosteroids were hydrocortisone, dexamethasone, and solone. No difference in mortality was found in the subgroups of hydrocortisone and methylprednisolone. A retrospective quasi-experimental study showed that dexamethasone is more effective in improving the PO2/FiO2 ratio of COVID-19 patients than methylprednisolone [32]. Another study also provided evidence that dexamethasone and betamethasone are effective for COVID-19 treatment because of their potential to inhibit the proteolytic activity of Mpro (a cysteine protease that plays a vital role in polyprotein processing and virus maturation) by comparing molecular docking studies of six corticosteroids (cortisone, hydrocortisone, prednisolone, methylprednisolone, betamethasone, and dexamethasone) and two repurposed drugs (darunavir and lopinavir) [33–36]. However, these survival benefits depended largely on the RECOVERY trial [11], which consisted of approximately 83.5% and 94.8%of the total number of patients in the analysis. if the RECOVERY trial excluded [11], these survival benefits were absent, more RCTs are needed in the future to draw definite conclusions.

The safety of corticosteroids in COVID-19 still is debated. Corticosteroid therapy attenuates the immune response, which increased the chance of infection and other adverse events [37]. In our study, seven studies reported the incidence rate of adverse events in COVID-19 patients (corticosteroid:7.0% vs control:5.9%) [10,18–21,23,24]. Four studies reported the incidence rate of nosocomial infections (corticosteroid:22.8% vs control:26.7%) [10,19–21]. There was no difference in the rates of adverse events and nosocomial infections between the corticosteroids group and the control group. One of 7 studies (GLUCOCOVID) showed that hyperglycemia (>180 mg/dl) was more frequent in the corticosteroid group in the ICU, with a significant difference [21]. Tomazini et al. [20] also reported unspecified hyperglycemia. Except for hyperglycemia, the incidence of adverse events was similar in either group. Similarly, a systematic review including peer-reviewed studies of any design reported that hyperglycemia was the most common adverse effect [38]. Therefore, when corticosteroids are used in clinical treatment, we need to pay more attention to blood sugar levels.

Kommentare zum Review

SR mit vergleichbarer Methodik und vergleichbaren Ergebnissen

- Li H et al., 2021 [21]. Effectiveness of corticosteroids to treat severe COVID-19: A systematic review and meta-analysis of prospective studies.
- Sterne JAC et al., 2020 [33]. Association Between Administration of Systemic Corticosteroids and Mortality Among Critically Ill Patients With COVID-19: A Meta-analysis.
- Abeldano Zuniga RA et al., 2021 [1]. Clinical effectiveness of drugs in hospitalized patients with COVID-19: a systematic review and meta-analysis.
- Boppana TK et al., 2021 [6]. Steroid therapy for COVID-19: A systematic review and meta-analysis of randomized controlled trials.
- Juul S et al., 2021 [16]. Interventions for treatment of COVID-19: Second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project)

Ngamprasertchai T et al., 2022 [26].

Efficacy and Safety of Immunomodulators in Patients with COVID-19: A Systematic Review and Network Meta-Analysis of Randomized Controlled Trials.

Fragestellung

We conducted a systematic review and network meta-analysis to rank immunomodulators in the treatment of COVID-19 according to their efficacy and safety.

Methodik

Population:

- adults aged ≥ 18 years who were hospitalized with COVID-19 infection and hyperinflammatory responses.

Intervention:

- corticosteroids, IL-6 inhibitors, IL-1 inhibitors, kinase inhibitors, immunomodulators
- Immunomodulators were classified by group as follows: IL antagonists, anakinra (ANA), sarilumab (SAR), and tocilizumab (TOC); corticosteroids, dexamethasone (DEX), hydrocortisone (HYD), and methylprednisolone (MET); and JAK inhibitors, baricitinib (BAR), ruxolitinib (RUX), and tofacitinib (TOF).

Komparator:

- placebo or standard of care (SOC)

Endpunkte:

- mortality rate, incidence of IMV, or risk of superimposed infection

Recherche/Suchzeitraum:

- We identified potential studies from MEDLINE via PubMed, SCOPUS, and clinical trial registries as well as the reference lists of selected studies published up to June 2021

Qualitätsbewertung der Studien:

- Risk of Bias 2.0 tool

Ergebnisse

Anzahl eingeschlossener Studien:

- 26 studies were included in the quantitative analysis. Ten treatments were analyzed: ANA, SAR, TOC, DEX, HYD, MET, BAR, RUX, TOF, and SOC.
- Corticosteroids were used as the SOC in some trials examining other treatments. The overall statistical heterogeneity was low according to the baseline severity (I2 = 0.0–10.0%; Figs. S1–3 in the supplementary material).

Charakteristika der Population:

Study	*N*	Intervention	Timing of intervention[b] (days)	Comparator	Severity[c]
Corticosteroids vs. SOC (*n* = 11)					
P. Horby [6], 2021 (Recovery)	6425	DEX (6 mg/day)	8.0 (5.0–13.0)	SOC	Mixed
H. Jamaati [35], 2021	50	DEX (10–20 mg/day)[e]	N/A	SOC	Mild to moderate
B. M. Tomazini [36], 2020 (CoDEX)	299	DEX (10–20 mg/day)[e]	9.0 (7.0–11.0)	SOC	Moderate to severe
J. Villar [37], 2020 (Dexa-COVID19 network)	200	DEX (10–20 mg/day)[e]	N/A	SOC	Moderate to severe
D. C. Angus [38], 2020 (The REMAP-CAP COVID-19)	384	HYD	1.2 (0.8–2.6)[i] Since hospital admission	SOC	Severe
P. F. Dequin [39], 2020 (CAPE COVID trial group)	149	HYD (50–200 mg/day)[f]	9.0 (7.0–11.5)	SOC	Critically ill
M. W. Petersen [40], 2020 (COVID STEROID)	30	HYD (200 mg/day)	4.0 (1.0–7.0) Since hospital admission	SOC	Severe
L. Corral-Gudino [41], 2021 (Glucocovid)	64	MET	12.0 ± 5.0	SOC	Moderate to severe

M. Edalatifard [42], 2020	72	MET (250 mg/day)	24–48 h after hospitalization	SOC	Severe
C. M. P. Jeronimo [24], 2020 (COVID-19; Metcovid)	393	MET (1 MKD)	13.0 (9.0–16.0)	SOC	Moderate to severe
X. Tang [43], 2021	86	MET (1 MKD)	8.0 (6.0–13.0)	SOC	Mixed
IL receptor antagonists vs. SOC (n = 10)					
RECOVERY [29], 2021	4116	TOC (8 MKD) 1–2 dose	9.0 (7.0–13.0)	SOC	Mixed
O. Hermine [44], 2021 (CORIMUNO-TOCI)	130	TOC (8 MKD)	10.0 (7.0–13.0)	SOC	Moderate to severe
O. Rosas [45], 2021 (COVACTA)	438	TOC (8 MKD)	11.0 (1.0–49.0)	SOC	Severe
C. Salama [46], 2021 (EMPACTA)	377	1–2 dose	N/A	SOC	Mixed
C. Salvarani [47], 2021 (RCT-TCZ-COVID-19)	126	TOC (8 MKD) 2 doses	7.0 (4.0–11.0)	SOC	Mild[d]
A.S. Soin [48], 2021 (COVINTOC)	179	TOC (6 MKD) 1–2 dose	N/A	SOC	Moderate to severe
J. H. Stone [49], 2020 (BACC bay)	242	TOC (8 MKD) Single dose	9.0 (6.0–13.0)	SOC	Mixed
V. C. Veiga [50], 2021	129	TOC (8 MKD) Single dose	10.0 ± 3.1	SOC	Severe to critical
F. X. Lescure [26], 2021	416	SAR (200–400 mg daily) 1–2 dose A second dose 8–24 h after first dose	SAR 200 mg 5.0 (2.0–10.0) SAR 400 mg 4.0 (2.0–9.0)	SOC	Severe to critical
CORIMUNO-19 collaborative group [51], 2021	114	ANA[g]	10.0 (8.0–13.0)	SOC	Mild to moderate
JAK inhibitors vs. placebo (n = 3)					
Y. Cao [52], 2020	41	RUX (5 mg twice a day)	N/A	SOC	Severe
A. C. Kalil [53], 2021	1033	BAR (4 mg/day) (2 mg/day if GFR < 60)	8.0 (5.0–10.0)	SOC	Moderate to severe

P.O. Guimaraes [54], 2021 (STOP-COVID)	289	TOF (10 mg twice daily)	10.0 (7.0–12.0)	SOC	Mixed
Others (n = 2)					
A.C. Gordon [22], 2021 REMAP-CAP	865	TOC (8 mg/kg) 1–2 dose or SAR (400 mg/day) single dose	TOC 1.2 (0.8–2.8) SAR 1.4 (0.9–2.8) Since hospital admission	SOC	Critically ill
K. Ranjbar [23], 2021	86	MET (2 mg/kg)	N/A	DEX (6 mg/day) 10 days	Severe

Qualität der Studien:

- The overall quality of the studies was rated as intermediate. Nine (34.6%) of the studies showed good quality which was noted for the randomization process and missing outcome data domains (88.5%). The lowest quality was noted for the deviations from intended interventions domain (50.0%). The study by Jeronimo [24] had a high risk of bias owing to missing outcome data

Studienergebnisse:

Direct Meta-analysis

- corticosteroids
  - The mortality rate among hospitalized patients was reduced by approximately 10.0% by treatment with corticosteroids (pooled RR 0.90; 95% CI 0.83–0.97; p\0.01) compared to SOC (Figs. S5–6). Corticosteroids decreased the incidence of IMV versus placebo, albeit without statistical significance
- IL antagonists
  - Although IL antagonists did not greatly reduce mortality rates, patients who received these immunomodulators had a significantly lower incidence of IMV versus SOC (pooled RR 0.79; 95% CI 0.70–0.89; p\0.01. The risk of superimposed infection was not significantly reduced by IL antagonists
- JAK Inhibitors
  - A nearly 40% reduction in the mortality rate was observed among patients treated with JAK inhibitors (pooled RR 0.61; 95% CI 0.38–0.95; Fig. S23). Patients treated with JAK inhibitors had a lower risk of superimposed infection than those treated with SOC without statistical significance

Network Meta-analysis

- Mortality Rate and Incidence of IMV
  - Mortality rate data from 26 studies (N = 16,733) consisting of 11 direct comparisons among 10 treatments were pooled. Data from 18 studies (N = 15,130) using direct comparisons among nine treatments were pooled for the incidence of IMV.
  - Overall, immunomodulators displayed better efficacy than SOC. Namely, DEX and TOC were linked to significantly lower mortality rates than SOC with pooled RRs of 0.91 (95% CI 0.84–0.99) and 0.88 (95% CI 0.82–0.96), respectively. Patients who received SAR, BAR,

or TOC exhibited a lower incidence of IMV than those treated with SOC with pooled RRs of 0.38 (95% CI 0.18–0.79), 0.68 (95% CI 0.46–0.93), and 0.78 (95% CI 0.70–0.87), respectively

- The relative treatment efficacy among corticosteroids demonstrated that HYD most strongly reduced the mortality rate reduction and incidence of IMV. MET tended to increase the mortality rate and incidence of IMV compared with the findings for HYD
- SAR was the most effective IL antagonist in terms of mortality and the incidence of IMV reduction. ANA had relatively worse efficacy than other the IL antagonists. Among JAK inhibitors, RUX had relatively better efficacy than the other treatments
- The highest probability of efficacy regarding the mortality rate as indicated by the highest SUCRA was identified for RUX, followed by TOF and BAR, whereas SAR had the greatest efficacy in terms of the incidence of IMV, followed by RUX and BAR

Anmerkung/Fazit der Autoren

We found in our systematic review that immunomodulators played a major role in the treatment of inflammatory responses associated with COVID-19. In comparison to SOC, immunomodulators reduced the mortality rate and incidence of IMV in RCTs of patients with mostly moderate-to-severe COVID-19.

Previous studies reported the efficacy of corticosteroids in the treatment of COVID-19. These drugs have emerged as the SOC for severe or critical COVID-19 on the basis of the results of the RECOVERY trial. Studies of IL antagonists or JAK inhibitors used corticosteroids as the SOC in some participants in the controlled arm. We were able to explore this effect using the results of treatment ranking based on the SUCRA score. Therefore, the ranking of ANA and TOF regarding the incidence of IMV should be interpreted with caution.

HYD and DEX tended to reduce the risks of mortality and IMV. However, we recorded higher rates of IMV and superimposed infection in patients with COVID-19 who received MET. Nevertheless, when we weigh the benefits and risks of MET, we strongly discourage its use regardless of the dose or regimen in clinical practice and further clinical studies. Although HYD was more effective than DEX in our network meta-analysis, a large-scale RCT following the protocol of the RECOVERY trial should be performed.

We observed little benefit of IL antagonists, contradicting the results of prior meta-analyses [15, 20] because we included a large-scale phase 3 RCT of SAR that reported a negative result [26]. IL antagonists significantly decreased the mortality rate and the incidence of IMV, primarily based on the effect of TOC, as reported previously [15, 16, 18]. Our network meta-analysis revealed that IL-6 antagonists (TOC or SAR) were superior to IL-1 antagonists in terms of mortality and IMV risk. We anticipate that IL-6 plays a greater role than IL-1 in the hyperinflammatory phase. In addition, IL-6 levels predict the possibility of IMV.

The efficacy of JAK inhibitors in our study was notable, particularly in terms of mortality. JAK inhibitors mitigate STAT3 hyperactivity, thereby improving immune dysregulation in severe COVID-19 [11]. In terms of the incidence of IMV, JAK inhibitors were inferior to other immunomodulators. Our findings were consistent with those of a previous meta-analysis [25]. Among JAK inhibitors, RUX was more beneficial than BAR concerning both mortality and IMV, but large-scale clinical trials are needed, as well as data for TOF. Considering the risk of superimposed infection, JAK inhibitors were superior to other treatments in all aspects. The risk–benefit ratio should be balanced for all immunomodulators.

Kommentare zum Review

Weitere Netzwerkmetaanalysen mit überwiegend in Deutschland derzeit nicht zugelassenen Arzneimitteln:

- Zhang C et al., 2021 [41]. Efficacy of COVID-19 Treatments: A Bayesian Network Meta-Analysis of Randomized Controlled Trials.
  - In this systematic review and NMA, we provided a detailed summary of trial characteristics of published RCTs for confirmed COVID-19 patients up to August 19, 2021 and reported effectiveness of treatments at both the drug and class levels in terms of mortality, mechanical ventilation, hospital discharge and viral clearance. Compared with SOC, imatinib, intravenous immunoglobulin and tocilizumab were shown to reduce the risk of mortality; baricitinib plus remdesivir, colchicine, dexamethasone, recombinant human GCSF and tocilizumab resulted in fewer events of mechanical ventilation; tofacitinib, sarilumab, remdesivir, tocilizumab and baricitinib plus remdesivir demonstrated their effectiveness with significantly higher 14-day hospital discharge rates.
  - At the class level of treatments, antineoplastic agents including bamlanivimab, imatinib and INM005 could reduce mortality; immunostimulants containing interferon beta and recombinant human GCSF showed clinical benefit over SOC in reducing mechanical ventilation; immunosuppressants consisting of canakinumab, sarilumab, tocilizumab and tofacitinib led to higher hospital discharge rates around 14 days, and the use of anthelmintics (ivermectin), anthelmintics plus antibacterials for systemic use (ivermectin plus doxycycline), endocrine therapy (proxalutamide) increased the rate of viral clearance on day 7. For other classes and outcomes, we observed no significant difference from SOC.
- Siemieniuk RA et al., 2020 [30]. Drug treatments for covid-19: living systematic review and network meta-analysis.
  - Corticosteroids probably reduce the risk of death and mechanical ventilation and probably increase ventilator-free days. The evidence for corticosteroids comes primarily from patients who are hypoxic and admitted to hospital. Whether corticosteroids have any important effect on patients with non-severe disease remains uncertain.
  - Interleukin-6 inhibitors are likely to have some benefits, although the evidence regarding their impact on mortality remains of low certainty. Other meta-analyses using fixed effects (that is, they do not consider between-trial heterogeneity) found a significant mortality reduction.105 223 Interleukin-6 inhibitors probably reduce risk of mechanical ventilation and may reduce duration of hospitalisation. The evidence for interleukin-6 inhibitors comes primarily from patients who are admitted to hospital and are hypoxic. The use (or not) of corticosteroids, and baseline C reactive protein levels did not appear to modify their effects, however data available for subgroup analyses was limited.
  - Whether or not remdesivir has any effect on mortality remains ncertain. If one believes the subgroup effect previously reported, remdesivir may reduce or have no effect mortality in patients with less severe disease and may increase or have no effect on mortality in patients with critical illness. The subgroup effect however has only moderate credibility and whether or not remdesivir reduces or increases mortality in any subgroup is uncertain. Remdesivir may reduce risk of mechanical ventilation.
  - Evidence from our analyses suggests that colchicine may reduce mortality, mechanical ventilation, and duration of hospitalisation
  - Two trials examined the effect of JAK inhibitors and appear to show promising results. JAK inhibitors may reduce mortality, mechanical ventilation, and duration of

hospitalisation. They probably reduce the duration of mechanical ventilation. Further trials are needed to confirm these promising effects.

- Full dose anticoagulation did not appear to show any important effect. A separate meta-analysis of four trials that examined full dose anticoagulation versus prophylactic dose anticoagulation appeared to show a reduction in mortality in patients with severe but not critical illness43; but these trials are not yet published in full and the data available is insufficient to judge whether or not it is a credible subgroup effect.
- Several interventions do not appear to have important impact on any patient-important outcomes, including angiotensin-converting enzyme inhibitors, azithromycin, hydroxychloroquine, interferon-beta, lopinavir-ritonavir, vitamin C, and vitamin D. For other interventions, there remains substantial uncertainty.

3.3 Leitlinien

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), 2021 [12].

S3-Leitlinie: Empfehlungen zur stationären Therapie von Patienten mit COVID-19. Stand: 28.02.2022

Zielsetzung/Fragestellung

Management stationäre Therapie von Patienten mit COVID-19.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu derzugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

LoE/GoR

- GRADE Methodik

Sonstige methodische Hinweise

Für diese Version der Leitlinie (Februar 2022) wurden zu den Themen Medikamentöse Therapie, Thromboembolieprophylaxe/Antikoagulation und Maßnahmen bei akuter hypoxämischer respiratorischer Insuffizienz systematische Recherchen durchgeführt. Übernommen wurden Empfehlungen zur medikamentösen ambulanten Therapie von der Leitlinie der DEGAM im Sinne einer Leitlinienadaptation (1). Neu erstellt wurden Evidenzsynthesen zu Nirmatrelvir/Ritonavir. Zu allen diesen Themen wurden Empfehlungen bestätigt, modifiziert oder neu abgestimmt. Die restlichen Empfehlungen wurden ebenfalls bestätigt. Die einzelnen Hintergrundtexte wurden aktualisiert. Änderungen zur Vorversion sind in roter Schriftfarbe.

Empfehlungen

3.3. Spezifische medikamentöse Therapie

Für die medikamentöse Therapie von COVID-19 gibt es antivirale und immunmodulatorische Ansätze, die sich jeweils in den frühen- oder späteren Krankheitsphasen bewährt haben. Diese aktualisierte Version der Leitlinie bezieht erstmalig auch ambulante Therapien mit ein (vgl. auch S2e-Leitlinie der DEGAM (1)), welche durch die Verfügbarkeit von wirksamen antiviralen Therapeutika, insbesondere in der Frühphase der Erkrankung, stark an Bedeutung gewonnen haben. Die Frühphase bezieht sich auf die ersten Tage nach dem Auftreten von Symptomen und erstreckt sich je nach Evidenzgrundlage bis zu einem Zeitraum von 5 bis 7 Tage nach Symptombeginn. Naturgemäß können Patienten aus unterschiedlichen Gründen bereits in der Frühphase mit oder wegen einer SARS-CoV-2-Infektion hospitalisiert sein, sodass eine strikte Unterteilung von ambulanten stationären Patienten in Bezug auf die Frühphase bei der Evidenzbewertung im Sinne der klinischen Praktikabilität weitgehend vermieden wurde.

Im Folgenden sind Therapien aufgeführt, die in einem randomisiert-kontrollierten Studiendesign untersucht und Studienergebnisse peer-reviewed veröffentlicht worden sind. Es wird darauf verwiesen, dass einige der empfohlenen Arzneimittel (noch) nicht zur Anwendung in der COVID-19 Therapie zugelassen sind (Off-Label Use). Neue, bislang nicht für COVID-19 oder andere Indikationen zugelassene Arzneimittel, können im Rahmen von Artikel 5 (3) der Verordnung 726/2004 des Europäischen Parlaments und der Medizinischer Bedarf Versorgungssicherstellungsverordnung (MedBVSV) nach Empfehlung der Europäischen Arzneimittelagentur (EMA) jedoch bereits vor einer Marktzulassung eingesetzt werden.

3.3.1. Zusammenfassende Empfehlungen

In der COVID-19 Frühphase können Patienten ohne Impfschutz mit mindestens einem Risikofaktor für einen schweren Verlauf antiviral behandelt werden, um dieses Risiko zu reduzieren. Zur Verfügung stehen aktuell SARS-CoV-2 neutralisierende monoklonale Antikörper (MAK), Remdesivir (≤ 7d nach Symptombeginn), Nirmatrelvir/Ritonavir (≤ 5d nach Symptombeginn) und Molnupiravir (≤ 5d nach Symptombeginn). Falls sich für eine Therapie entschieden wird, erfolgt diese als Einzelfallentscheidung unter Einbeziehung von Verfügbarkeit, Kontraindikationen, Hospitalisierungsstatus und individuellem Patientenrisiko. Immunsupprimmierte Patienten, bei denen eine relevante Beeinträchtigung der Impfantwort bzw. humoralen Immunantwort besteht (15), sollten vorzugsweise mit MAK behandelt werden, welche nachweislich gegen die aktuell (02/2022) zirkulierenden Virusvarianten (einschl. Omikron) wirksam sind. Derzeit in Deutschland verfügbar und Omikron-wirksam ist der MAK Sotrovimab. Alle Patienten mit mindestens Low-Flow-Sauerstoff-Bedarf oder schwererem Erkrankungsverlauf sollen Dexamethason erhalten (WHO Skala 5-9). Patienten mit Low-Flow- oder High-Flow-Sauerstofftherapie (WHO Skala 5-6) können zusätzlich mit dem JAK-1 Antagonist Baricitinib behandelt werden. Ein klinischer Nutzen einer Therapie mit dem IL-6-Antagonisten Tocilizumab ist nur bei Patienten mit Sauerstoffbedarf und rasch progredientem Krankheitsverlauf hin zum respiratorischen Versagen (WHO Skala (5)/(6) zu erwarten. Tocilizumab soll unter keinen Umständen zusammen mit JAK-Inhibitoren wie Baricitinib eingesetzt werden. Der Nutzen oder Schaden einer sequentiellen Therapie wurde in klinischen Studien nicht geprüft. Der klinische Nutzen von Remdesivir bei Patienten mit Low-Flow- und High-Flow-Sauerstoff bis hin zur nicht-invasiven Beatmung (WHO Skala 5-6) bleibt auf Grundlage der vorliegenden Evidenz aus randomisiert kontrollierten Studien weiterhin unsicher. Bei Patienten mit invasiver Beatmung (WHO Skala 7-9) soll Remdesivir nicht eingesetzt werden.

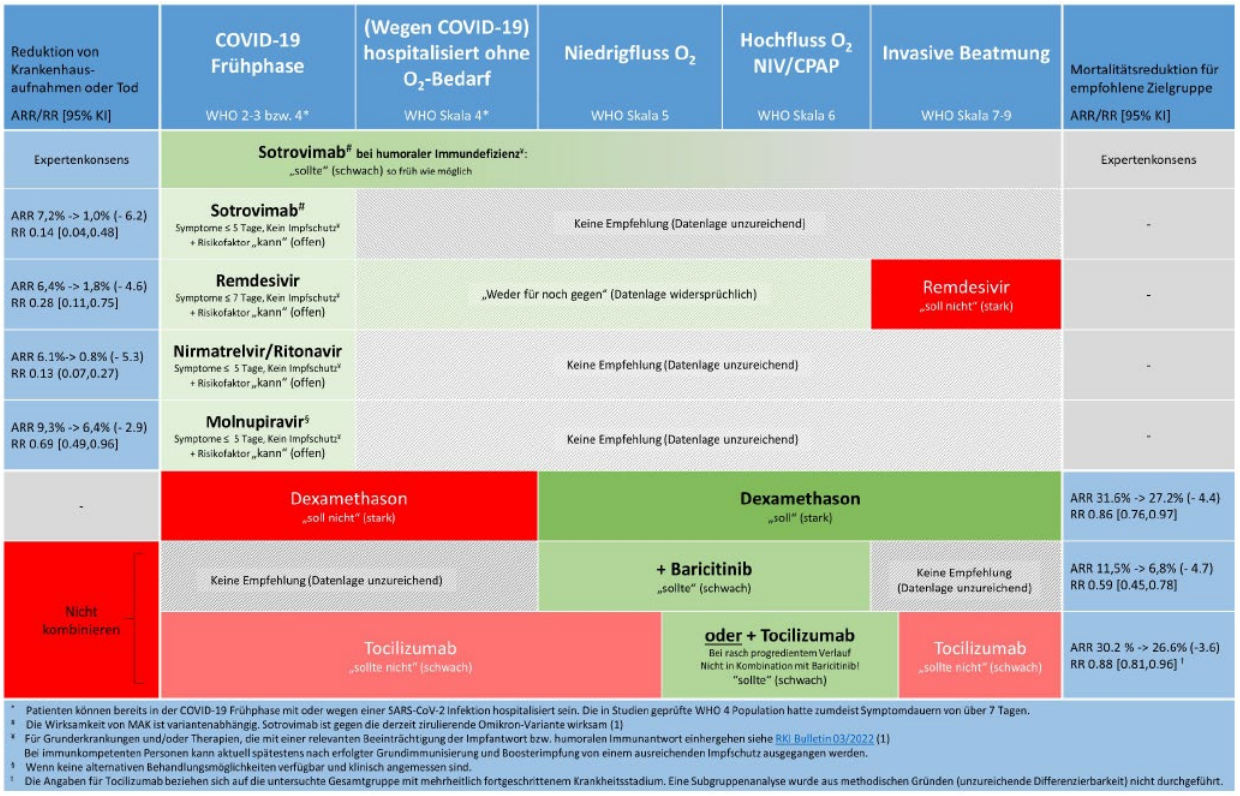


Abbildung 1: Übersicht der Empfehlungen der medikamentösen Therapie bei COVID-19, abhängig von der Krankheitsschwere.

3.3.2. Antivirale Therapieansätze

3.3.2.1. Monoklonale Antikörper

3.3.2.2. Sotrovimab

EMPFEHLUNG 1	**Evidenzbasierte Empfehlung, neu 02/2022**
Empfehlungsgrad: 0 ⇔	**a) Sotrovimab kann bei Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, in der Frühphase der Erkrankung (≤ 5 Tage nach Symptombeginn) eingesetzt werden.**
	Empfehlung (EK), neu 02/2022
EK	**b) Immunsupprimierte Patienten mit COVID-19 mit hohem Risiko für einen schweren Verlauf, bei denen eine relevante Beeinträchtigung der Impfantwort zu erwarten ist, sollten innerhalb von 5 Tagen nach Symptombeginn mit Sotrovimab behandelt werden (Expertenkonsens).**
Qualität der Evidenz: **Frühphase** Hospitalisierung/Tod: moderat ⊕⊕⊕⊖ 28-Tage-Sterblichkeit: niedrig ⊕⊕⊖⊖	Literatur: Gupta A et al. N Engl J Med. 2021 Nov 18;385(21):1941-1950. doi: 10.1056/NEJMoa2107934. Self WH et al. Lancet Infect Dis. 2021 Dec 23;S1473-3099(21)00751-9. doi: 10.1016/S1473-3099(21)00751-9.
	Starker Konsens

3.3.2.3. Remdesivir

EMPFEHLUNG 2	**Evidenzbasierte Empfehlung, aktualisiert 02/2022**
Empfehlungsgrad: **0 ⇔**	a) Remdesivir kann bei Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, in der Frühphase (≤ 7 Tage nach Symptombeginn) eingesetzt werden.
	Ergänzende Empfehlung (EK), neu 02/2022
EK	b) Immunsupprimierte Patienten mit COVID-19, bei denen eine relevante Beeinträchtigung der Impfantwort besteht, können mit Remdesivir behandelt werden, wenn keine wirksame Therapie mit monoklonalen Antikörpern verfügbar ist (Expertenkonsens).
	Evidenzbasiertes Statement, modifiziert 02/2022
	c) Es kann keine Empfehlung für oder gegen Remdesivir bei hospitalisierten Patienten mit COVID-19 Pneumonie und Low-Flow-Sauerstofftherapie abgegeben werden.
	Evidenzbasierte Empfehlung bestätigt 02/2022
Empfehlungsgrad: **A ⇓⇓**	d) Remdesivir soll nicht bei COVID-19-Patienten mit invasiver Beatmung eingesetzt werden.

Qualität der Evidenz: **Frühphase** Hospitalisierung/Tod bis Tag 28: moderat ⊕⊕⊕⊖ **Fortgeschrittene Erkrankung (stationär)** 28-Tage-Sterblichkeit: moderat ⊕⊕⊕⊖ Klinische Verschlechterung (Invasive Beatmung): Niedrig ⊕⊕⊖⊖	Literatur: Gottlieb R.L. et al. N Engl J Med. 2022 Jan 27;386(4):305-315. doi: 10.1056/NEJMoa2116846 Ansems K. et al. Cochrane Database Syst Rev. 2021 Aug ;8(8):CD014962.doi: 10.1002/14651858.CD014962 Ader F et al. Lancet Infect Dis. 2022 Feb;22(2):209-221. doi: 10.1016/S1473-3099(21)00485-0 Ali K et al. CMAJ. 2022 Jan 19;cmaj.211698. doi: 10.1503/cmaj.211698
	a-d) Starker Konsens

3.3.2.4. Nirmatrelvir/Ritonavir

EMPFEHLUNG 3	**Evidenzbasierte Empfehlung, neu 02/2022**
Empfehlungsgrad: **0 ⇔**	**Nirmatrelvir/Ritonavir kann bei erwachsenen Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, innerhalb der ersten 5 Tage nach Symptombeginn eingesetzt werden.** Hinweis: Aufgrund des hohen Wechselwirkungspotentials müssen relevante Interaktionen mit bestehender Medikation zwingend vor Therapiebeginn überprüft werden.
Qualität der Evidenz: **Frühphase** 28-Tage-Sterblichkeit: niedrig ⊕⊕⊖⊖ Hospitalisierung/Tod bis Tag 28: niedrig ⊕⊕⊖⊖	Literatur: Hammond J et al. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542

Unerwünschte Ereignisse: moderat ⊕⊕⊕⊖	
	Starker Konsens

3.3.2.5. Molnupiravir

EMPFEHLUNG 4	Evidenzbasierte Empfehlung, neu 02/2022
Empfehlungsgrad: 0 ⇔	Molnupiravir kann, wenn keine alternativen Behandlungsmöglichkeiten verfügbar und klinisch angemessen sind, bei Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, innerhalb der ersten 5 Tage nach Symptombeginn eingesetzt werden. Eine Schwangerschaft muss ausgeschlossen werden. Eine Aufklärung über die Teratogenität und potenzielle Mutagenität von Molnupiravir ist obligat.
Qualität der Evidenz: **Frühphase** 29-Tage-Sterblichkeit: niedrig ⊕⊕⊖⊖ Hospitalisierung/Tod bis Tag 29: sehr niedrig ⊕⊖⊖⊖ Unerwünschte Ereignisse: moderat ⊕⊕⊕⊖	Literatur: Bernal AJ et al. N Engl J Med. 2022 Feb 10;386(6):509-520. doi: 10.1056/NEJMoa2116044 Caraco J et al. NEJM Evid 2021 Dec 16. doi: 10.1056/EVIDoa2100043 Fischer WA et al. Sci Transl Med. 2022 Jan 19;14(628):eabl7430. doi: 10.1126/scitranslmed.abl7430 Khoo SH et al. J Antimicrob Chemother. 2021 Nov 12;76(12):3286-3295. doi: 10.1093/jac/dkab318 Arribas JR et al. NEJM Evid 2021 Dec 16. doi: 10.1056/EVIDoa2100044
	Starker Konsens

3.3.3. Immunmodulatorische Therapieansätze

3.3.3.1 Kortikosteroide

EMPFEHLUNG 5	Evidenzbasierte Empfehlung, aktualisiert 02/2022
Empfehlungsgrad: A ⇑⇑	Bei Patienten mit COVID-19 und Low-Flow/High-Flow-Sauerstofftherapie oder nicht-invasiver/invasiver Beatmung soll eine Therapie mit systemischen Kortikosteroiden erfolgen. Die Therapie sollte mit 6 mg Dexamethason p.o. oder i.v. über zehn Tage erfolgen.
A⇓⇓	Bei Patienten mit milder bis moderater Erkrankung ohne Notwendigkeit einer Sauerstoffgabe soll keine Therapie mit systemischen Kortikosteroiden erfolgen
Qualität der Evidenz: 30-Tage Sterblichkeit: moderat ⊕⊕⊕⊖ Unerwünschte Ereignisse: Sehr niedrig ⊕⊖⊖⊖	Literatur: Horby P. et al. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436 Tomazini BM et al. JAMA. 2020 Oct 6;324(13):1307-1316. doi: 10.1001/jama.2020.17021 Edalatifard M et al. Eur Respir J. 2020 Dec 24;56(6):2002808. doi: 10.1183/13993003.02808-2020 Dequin PF et al. JAMA. 2020 Oct 6;324(13):1298-1306. doi: 10.1001/jama.2020.16761 Jeronimo CMP et al. Clin Infect Dis. 2021 May 4;72(9):e373-e381. doi: 10.1093/cid/ciaa1177 Angus DC et al. JAMA. 2020 Oct 6;324(13):1317-1329. doi: 10.1001/jama.2020.17022 Wagner C et al. Cochrane Database Syst Rev. 2021 Aug 16;8(8):CD014963. doi: 10.1002/14651858.CD014963
	Starker Konsens

3.3.3.2 Baricitinib

EMPFEHLUNG 6	**Evidenzbasierte Empfehlung, aktualisiert 02/2022**
Empfehlungsgrad: B ⇑	**Baricitinib sollte bei Patienten mit COVID-19 Pneumonie und Low-Flow-/High-Flow--Sauerstofftherapie oder nicht-invasiver Beatmung unter Beachtung der Kontraindikationen eingesetzt werden.**
A ⇓⇓	**Baricitinib soll nicht als Kombinationstherapie mit Tocilizumab eingesetzt werden.**
Qualität der Evidenz: 28-Tage-Sterblichkeit: hoch ⊕⊕⊕⊕ 60-Tage-Sterblichkeit: moderat ⊕⊕⊕⊖ Klinische Verschlechterung/Tod: moderat ⊕⊕⊕⊖ Unerwünschte Ereignisse (alle Grade und SAE): hoch ⊕⊕⊕⊕	Literatur: Kalil A et al. N Engl J Med. 2021 Mar 4;384(9):795-807. doi: 10.1056/NEJMoa2031994. Epub 2020 Dec 11 Marconi VC. Et al. Lancet Respir Med. 2021 Aug 31;S2213-2600(21)00331-3. doi: 10.1016/S2213-2600(21)00331-3 Ely EW. Lancet Respir Med. 2022 Feb 3;S2213-2600(22)00006-6. doi: 10.1016/S2213-2600(22)00006-6 Andere JAK-I: Guimarães PO et al. N Engl J Med. 2021 Jul 29;385(5):406-415. doi: 10.1056/NEJMoa2101643. Epub 2021 Jun 16
Spezielle AE (Sekundärinfektion): niedrig ⊕⊕⊖⊖	Cao Y et al. J Allergy Clin Immunol. 2020 Jul;146(1):137-146.e3. doi: 10.1016/j.jaci.2020.05.019. Epub 2020 May 26
	Starker Konsens

3.3.3.3 Tocilizumab (TCZ)

EMPFEHLUNG 7	**Evidenzbasierte Empfehlung, bestätigt 02/2022**
Empfehlungsgrad: B⇑	**Tocilizumab sollte bei COVID-19-Patienten mit progredient schwerer Erkrankung zur COVID-19-Behandlung verabreicht werden.**
B⇓	**Tocilizumab sollte nicht eingesetzt werden bei Erkrankung ohne oder mit niedrigem Sauerstoffbedarf sowie bei bestehender invasiver Beatmung.**
A ⇓⇓	**Tocilizumab soll nicht als Kombinationstherapie mit JAK-Inhibitoren angewendet werden.**
Qualität der Evidenz: 28 Tage Sterblichkeit: moderat ⊕⊕⊕⊖ Vermeidung der Zunahme der Krankheitsschwere (Progress zu notwendiger Invasiver Beatmung): moderat ⊕⊕⊕⊖ Schwere unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖ Unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖	Literatur: Abani O et al. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0 Gordon AC et al. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433 Rosas IO et al. N Engl J Med. 2021 Apr 22;384(16):1503-1516. doi: 10.1056/NEJMoa2028700 Ghosn L et al. Cochrane Database Syst Rev. 2021 Mar 18;3(3):CD013881. doi: 10.1002/14651858.CD013881
	Starker Konsens

3.3.3.4 Anakinra

STATEMENT	Evidenzbasiertes Statement, aktualisiert 02/2022
	Bei hospitalisierten Patienten mit COVID-19 kann weder eine Empfehlung für noch gegen eine Therapie mit Anakinra gegeben werden.
Qualität der Evidenz: 28-Tage-Sterblichkeit: moderat ⊕⊕⊕⊖	Literatur: Tharaux, P. et al. Lancet Respir Med. 2021 Mar;9(3):295-304. doi: 10.1016/S2213-2600(20)30556-7. Epub 2021 Jan 22. Declercq J et al. Lancet Respir Med. 2021 Dec;9(12):1427-1438. doi: 10.1016/S2213-2600(21)00377-5.
Progression (Invasive Beatmung oder Tod): moderat ⊕⊕⊕⊖	Kharazmi et al. Immun Inflamm Dis. 2022 Feb; 10(2): 201–208. doi: 10.1002/iid3.563 Kyriazopoulou et al. Nat Med. 2021 Oct;27(10):1752-1760. doi: 10.1038/s41591-021-01499-z.
	Starker Konsens

3.3.4. Nicht empfohlene Medikamente

MEDIKAMENTÖSE INTERVENTION	Empfehlung bei hospitalisierten Patienten mit COVID-19	Mortalitätsreduktion absolut und Relatives Risiko (CI 95%)	Quality of evidence (bzgl. Mortalität)
Rekonvaleszentenplasma	Soll nicht	23,7% –> 23,3% RR 0.98 (0.92 – 1.05)	High
Ivermectin	Soll nicht	9,6% –> 5,8% RR 0.6 (0,14 – 2.51)	Very low
Vit D	Soll nicht	Not pooled/MA (heterogeneity)	k.A. (wenige pat-relevante Endpunkte untersucht)
Azithromycin	Soll nicht	22,3% –> 21,9% RR 0.98 (0.9 – 1.06)	High
Colchicin	Soll nicht	20,7% –> 20,7% RR 1 (0.93 – 1.08)	Moderate

Zusätzliche Informationen aus DEGAM, 2022 [11]. SARS-CoV-2/Covid-19-Informationen & Praxishilfen für niedergelassene Hausärztinnen und Hausärzte

Pharmakologische Therapie

8.1 Budesonid-Inhalation als Therapie

8.1.1 Empfehlung

Patientinnen und Patienten mit SARS-CoV-2-Infektion und Risiko für einen schweren Verlauf kann eine Budesonid-Inhalation: 2 x 800 µg/d für 7-14 Tage zur Senkung dieses Risikos angeboten werden (Off-label-Therapie).

Abstimmung DEGAM: 7 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung
Abstimmung: DGI, DGPI, DGIM, DGP, DGIIN, DGRh, DAIG, DGKJ, Patientenvertreterinnen: 4 ja, 5 nein, 1 Enthaltung; 44 % Zustimmung (nicht angenommen)

Qualität der Evidenz		Empfehlungsgrad
Mortalität	⊕⊕⊖⊖ **(niedrig)**	**0**
Hospitalisierung oder Tod	⊕⊕⊕⊖ **(moderat)**	
Verkürzung der Symptomdauer	⊕⊕⊖⊖ **(niedrig)**	
Symptomauflösung	⊕⊕⊕⊖ **(moderat)**	
Lebensqualität	⊕⊕⊖⊖ **(niedrig)**	

[1] Ramakrishnan et al., 2021 (STOIC Trial), [2] Yu et al., 2021 (PRINCIPLE Trial), [3] Clemency et al., 2021

8.1.2 Sondervotum
von DGI, DGPI, DGIM, DGP, DGIIN, DGRh, DAIG, DGKJ
Es kann weder eine Empfehlung für noch gegen Budesonid-Inhalation bei Patientinnen und Patienten mit SARS-CoV-2 Infektion abgegeben werden.
Abstimmung: DGI, DGPI, DGIM, DGP, DGIIN, DGRh, DAIG, DGKJ, Patientenvertreterinnen: 9 ja, 0 nein, 0 Enthaltung; 100 % Zustimmung
Abstimmung DEGAM: 0 ja, 7 nein, 0 Enthaltungen; 100 % Ablehnung

Statement

Sotrovimab als Therapie

8.2.1 Empfehlung	Empfehlungsgrad
Sotrovimab kann bei Patientinnen und Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, innerhalb von 5 Tagen nach Symptombeginn eingesetzt werden. Abstimmung: 17 ja, 0 nein, 2 Enthaltungen; 100 % Zustimmung	0
8.2.2 Empfehlung **Immunsupprimierte Patientinnen und Patienten mit COVID-19 mit hohem Risiko für einen schweren Verlauf, bei denen eine relevante Beeinträchtigung der Impfantwort zu erwarten ist, sollten innerhalb von 5 Tagen nach Symptombeginn mit Sotrovimab behandelt werden.** Abstimmung: 17 ja, 0 nein, 2 Enthaltungen wegen Interessenkonflikt; 100 % Zustimmung	B

Qualität der Evidenz	
Mortalität	⊕⊕⊖⊖ **(niedrig)**
Hospitalisierung oder Tod	⊕⊕⊕⊖ **(moderat)**
Sauerstofftherapiebedarf	⊕⊕⊕⊖ **(moderat)**
Unerwünschte Ereignisse Grad 3-4	⊕⊕⊕⊖ **(moderat)**
Schwerwiegende unerwünschte Ereignisse	⊕⊕⊕⊖ **(moderat)**

[4] Gupta A et al., 2021 (COMET-ICE), [5] Kreuzberger N et al., 2021

8.3 Remdesivir als Therapie

8.3 Empfehlung
Remdesivir kann bei Patientinnen und Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, eingesetzt werden. Immunsupprimierte Patientinnen und Patienten mit COVID-19, bei denen eine relevante Beeinträchtigung der Impfantwort besteht, können mit Remdesivir behandelt werden, wenn keine wirksame Therapie mit monoklonalen Antikörpern verfügbar ist.

Beginn der Therapie innerhalb von 7 Tagen nach Symptombeginn; die Therapie ist am ehesten in spezialisierten Zentren durchführbar, z. B. in an Kliniken angebundenen Ambulanzen, ggf. Corona-Schwerpunktpraxen oder stationär.*

Abstimmung: 14 ja, 1 nein, 1 Enthaltung wegen Interessenkonflikt; 95 % Zustimmung

Qualität der Evidenz		Empfehlungsgrad
Hospitalisierung oder Tod	⊕⊕⊕⊖ **(moderat)**	0
Unerwünschte Ereignisse (alle)	⊕⊕⊕⊖ **(moderat)**	
Schwerwiegende unerwünschte Ereignisse	⊕⊕⊖⊖ **(niedrig)**	

[6] Gottlieb et al., 2021

*Erläuterung: Da Remdesivir an drei hintereinander folgenden Tagen intravenös (jeweils eine Stunde) verabreicht werden muss, stößt die Anwendung in der hausärztlichen Praxis auf logistische Probleme.

8.4 Fluvoxamin als Therapie

8.4 Statement

Es kann weder für noch gegen den Einsatz von Fluvoxamin eine Empfehlung abgegeben werden. (Off-label-Therapie)

Qualität der Evidenz	
Mortalität	⊕⊕⊕⊖ (moderat)
Besuch Notaufnahme und/oder Krankenhausaufenthalt	⊕⊕⊕⊖ (moderat)

[7] Lenze EJ et al., 2020, [8] Reis G et al., 2021 (TOGETHER Trial)

8.6 Molnupiravir als Therapie

8.6 Empfehlung

Molnupiravir kann, wenn keine alternativen Behandlungsmöglichkeiten verfügbar und klinisch angemessen sind, bei erwachsenen Patientinnen und Patienten mit COVID-19, bei denen kein Impfschutz und mindestens ein Risikofaktor für einen schweren Verlauf vorliegt, innerhalb der ersten 5 Tage nach Symptombeginn eingesetzt werden.

Eine Schwangerschaft muss ausgeschlossen werden. Eine Aufklärung über die Teratogenität und potenzielle Mutagenität von Molnupiravir ist obligat.

Abstimmung: 14 ja, 3 nein, 2 Enthaltungen wegen Interessenkonflikt; 82 % Zustimmung

Qualität der Evidenz		Empfehlungsgrad
Mortalität	**⊕⊕⊖⊖ (niedrig)**	**0**
Hospitalisierung oder Tod	**⊕⊖⊖⊖ (sehr niedrig)**	
Unerwünschte Ereignisse	**⊕⊕⊕⊖ (moderat)**	
Schwerwiegende unerwünschte Ereignisse	**⊕⊕⊕⊖ (moderat)**	

[14] Khoo SH et al., 2021, [15] Fischer II WA et al., 2022, [16] Caraco Y et al., 2021, [17] Bernal AJ et al., 2021

8.8 Azithromycin als Therapie

8.8 Empfehlung

Azithromycin soll im ambulanten Bereich nicht zur Behandlung einer COVID-19-Erkrankung eingesetzt werden.
Abstimmung: 16 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung

Qualität der Evidenz		Empfehlungsgrad
Mortalität	⊕⊕⊖⊖ (niedrig)	A
Hospitalisierung oder Tod	⊕⊕⊖⊖ (niedrig)	
Verbesserung des klinischen Status Tag 14	⊕⊕⊕⊕ (hoch)	
Unerwünschte Wirkungen jeder Schwere	⊕⊕⊖⊖ (niedrig)	

[24] Popp M et al., Antibiotics for the treatment of COVID-19. Cochrane Review darin: [25] Omrani AS et al., 2020, [26] Hinks TSC et al., 2021, [27] Johnston C et al., 2021, [28] Oldenburg CE et al., 2021, [29] Principle Trial Collaborative Group, Butler CC et al., 2021

8.9 Ivermectin als Therapie

8.9 Empfehlung

Ivermectin soll im ambulanten Bereich nicht zur Behandlung einer COVID-19-Erkrankung eingesetzt werden.
Abstimmung: 16 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung

Qualität der Evidenz		Empfehlungsgrad
Mortalität	⊕⊕⊖⊖ (niedrig)	A
Verschlechterung klinischer Status	⊕⊕⊖⊖ (niedrig)	
Virale Clearance an Tag 7	⊕⊖⊖⊖ (sehr niedrig)	

[30] Ahmed S et al., 2021, [31] López-Medina E et al., 2021, [32] Chaccour C et al., 2021, [33] Chachar AZK et al., 2020, [34] Podder CS et al., 2020, [35] Kishoria N et al., 2020, [36] Vallejos J et al., 2021 in: [37] Popp M et al., Ivermectin for preventing and treating COVID-19. 2021 Cochrane Review

8.10 Acetylsalicylsäure als Therapie

8.10 Empfehlung

Acetylsalicylsäure soll im ambulanten Bereich zur Therapie von an COVID-19 erkrankten Patientinnen und Patienten nicht eingesetzt werden.
Abstimmung: 16 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung

Qualität der Evidenz		Empfehlungsgrad
Mortalität	⊕⊖⊖⊖ (sehr niedrig)	A
Hospitalisierung oder Tod	⊕⊖⊖⊖ (sehr niedrig)	
Jegliches thrombotische Ereignis	⊕⊖⊖⊖ (sehr niedrig)	
Schwere Blutung	⊕⊕⊖⊖ (niedrig)	

[38] Connors JM et al., 2021

8.11 Colchicin als Therapie

8.11 Statement

Für Colchicin kann im ambulanten Bereich zur Therapie einer COVID-19 Erkrankung keine Empfehlung abgegeben werden.
Abstimmung: 16 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung

Qualität der Evidenz	
Mortalität	⊕⊕⊖⊖ (niedrig)
Hospitalisierung oder Tod	⊕⊕⊕⊖ (moderat)
Schwerwiegende unerwünschte Ereignisse	⊕⊕⊕⊖ (moderat)
Behandlungsbezogene unerw. Ereignisse	⊕⊕⊖⊖ (niedrig)

[39] Mikolajewska A et al, Colchicine for the treatment of COVID-19. Cochrane Review 2021

8.12 Systemische Steroide als Therapie

8.12 Empfehlung

Systemische Steroide sollen nicht zur COVID-19 Therapie im ambulanten Bereich eingesetzt werden.
Abstimmung: 16 ja, 0 nein, 0 Enthaltungen; 100 % Zustimmung

Empfehlungsgrad
Expertenkonsens

[40] Wagner C et al., 2021

Infectious Diseases Society of America (IDSA), 2022 [15]

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 8.0.0

Zielsetzung/Fragestellung

Develop evidence-based rapid guidelines intended to support patients, clinicians and other health-care professionals in their decisions about treatment and management of patients with COVID-19.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: kein Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Ovid Medline and Embase were searched through March 31, 2021
- Letzte Aktualisierung: March 23, 2022

LoE/GoR

- Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs and the Risk of Bias Instrument for Non-randomized Studies - of Interventions (ROBINS-I)
- Grading of Recommendations Assessment, Development, and Evaluation (GRADE)
- As per GRADE methodology, recommendations are labeled as “strong” or “conditional”. The words “we recommend” indicate strong recommendations and “we suggest” indicate conditional recommendations. Abbildung 1 provides the suggested interpretation of strong and weak recommendations for patients, clinicians, and healthcare policymakers. For recommendations where the comparators are not formally stated, the comparison of interest is implicitly referred to as “not using the intervention”. These recommendations acknowledge the current “knowledge gap” and aim at avoiding premature favorable recommendations for their use and to avoid encouraging the rapid diffusion of potentially ineffective orharmful interventions.

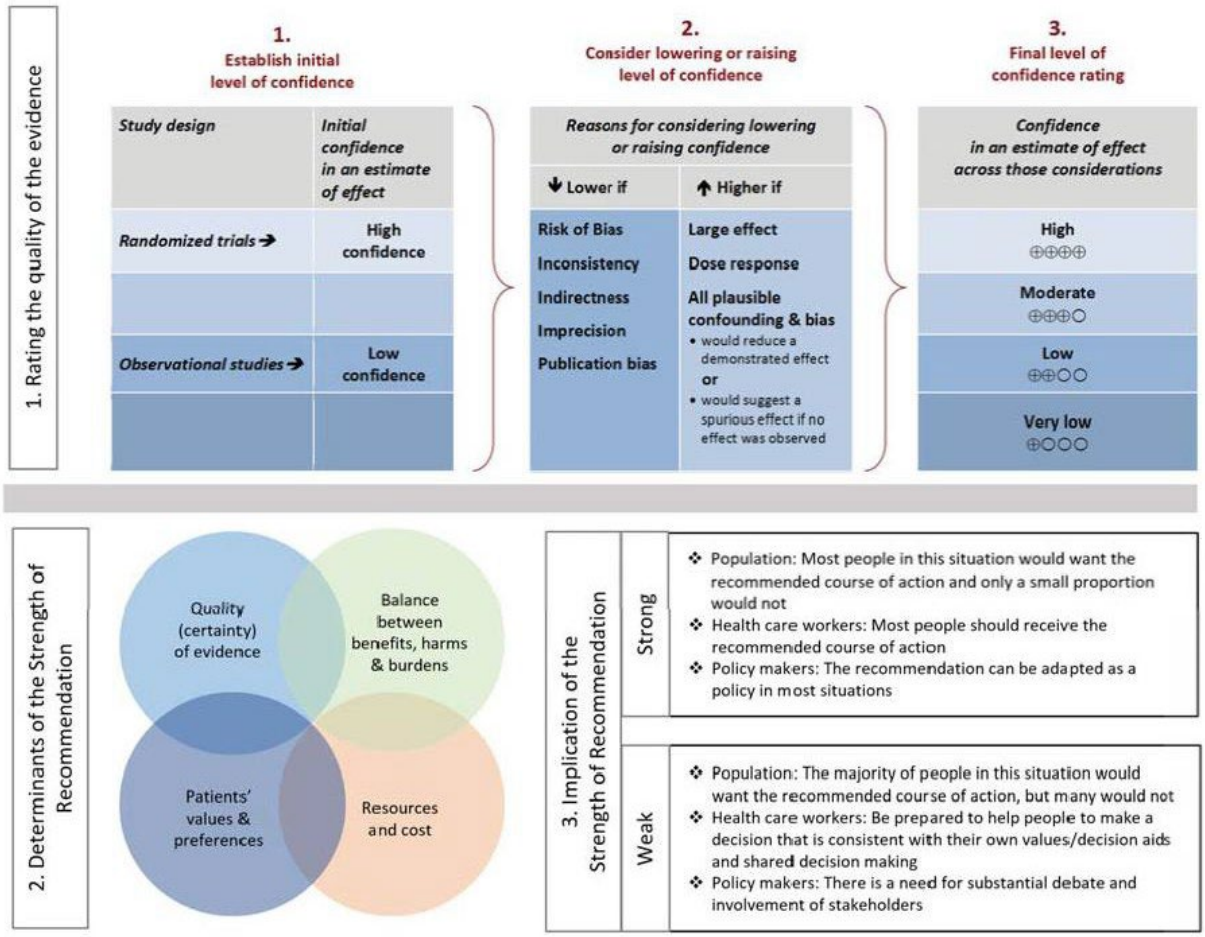


Abbildung 1: Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)

Sonstige methodische Hinweise

- In addition, given the need for an urgent response to a major public health crisis, the methodological approach was modified according to the Guidelines International Network/McMaster checklist for the development of rapid recommendations.
- For several interventions, no direct evidence was available other than case reports or mechanistic considerations. The panel either decided to include plausible indirect evidence and make a recommendation (e.g., from studies of SARS-CoV) or to provide a short narrative discussion of the intervention.
- This is a living guideline that will be frequently updated as new data emerges. Updates and changes to the guideline will be posted to the IDSA website.

EMPFEHLUNGEN

Hydroxychloroquine/Chloroquine; Hydroxychloroquine/Chloroquine plus Azithromycin

Section last reviewed and updated 12/23/2020

Last literature search conducted 12/14/2020

- Recommendation 1: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine*. (Strong recommendation, Moderate certainty of evidence)
  - Remark: Chloroquine is considered to be class equivalent to hydroxychloroquine.
- Recommendation 2: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against hydroxychloroquine* plus azithromycin. (Strong recommendation, Low certainty of evidence)
  - Remark: Chloroquine is considered to be class equivalent to hydroxychloroquine.

Lopinavir/Ritonavir

Section last reviewed and updated 2/16/2022

Last literature search conducted 1/31/2022

- Recommendation 4: In persons exposed to COVID-19, the IDSA guideline panel recommends against post-exposure prophylaxis with lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)
- Recommendation 5: Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends against the use of lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)
- Recommendation 6: Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against the use of the combination lopinavir/ritonavir. (Strong recommendation, Moderate certainty of evidence)

Glucocorticoids

Section last reviewed and updated 9/25/2020

Last literature search conducted 9/4/2020

- Recommendation 7: Among hospitalized critically ill patients* with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)
  - Remark: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
- Recommendation 8: Among hospitalized patients with severe**, but non-critical, COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)
  - Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
- Recommendation 9: Among hospitalized patients with non-severe*** COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)

Inhaled Corticosteroids

Section last reviewed and updated 3/14/2022

Last literature search conducted 2/28/2022

- Recommendation 10 (NEW 3/14/2022): Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel suggests against inhaled corticosteroids outside of the context of a clinical trial. (Conditional recommendation, Moderate certainty of evidence)

Interleukin-6 Inhibitors

Section last reviewed and updated on 9/14/2021

Last literature search conducted 8/31/2021

- Recommendation 11: Among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Low certainty of evidence)
  - Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of tocilizumab and a low value on the uncertain mortality reduction, would reasonably decline tocilizumab.
  - In the largest trial on the treatment of tocilizumab, criterion for systemic inflammation was defined as CRP ≥75 mg/L.
- Recommendation 12: When tocilizumab is not available for patients who would otherwise qualify for tocilizumab, the IDSA guideline panel suggests sarilumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (Conditional recommendation, Very low certainty of evidence)
  - Remark: Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of sarilumab and a low value on the uncertain mortality reduction, would reasonably decline sarilumab.

Convalescent Plasma

Section last reviewed and updated 2/3/2022

Last literature search conducted 1/31/2022

- Recommendation 13: Among patients hospitalized with COVID-19, the IDSA guideline panel recommends against COVID-19 convalescent plasma. (Strong recommendation, Moderate certainty of evidence)
- Recommendation 14: Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)
  - In the United States, FDA EUA only authorizes use in patients with immunosuppressive disease or receiving immunosuppressive treatment.
  - Patients, particularly those who are not immunocompromised, who place a low value on the uncertain benefits (reduction in the need for mechanical ventilation, hospitalization, and death) and a high value on avoiding possible adverse events associated with convalescent plasma would reasonably decline convalescent plasma.

Remdesivir

Section last reviewed and updated 2/7/2022

Last literature search conducted 1/31/2022

- Recommendation 15: Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests remdesivir initiated within seven days of symptom onset rather than no remdesivir. (Conditional recommendation, Low certainty of evidence)
  - Dosing for remdesivir is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.
  - Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, molnupiravir, and neutralizing monoclonal antibodies. Patient specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.
- Recommendation 16: In patients on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)
- Recommendation 17a: In hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (Conditional recommendation, Moderate certainty of evidence)

**Severe illness is defined as patients with SpO2 ≤94% on room air.*

- Recommendation 17b: In patients with COVID-19 on invasive ventilation and/or ECMO, the IDSA panel suggests against the routine initiation of remdesivir (Conditional recommendation, Very low certainty of evidence)

Famotidine

Section last reviewed and updated 6/22/2020

Last literature search conducted 6/18/2020

- Recommendation 18: Among hospitalized patients with severe COVID-19, the IDSA panel suggests against famotidine use for the sole purpose of treating COVID-19 outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

The last literature search was conducted on June 18, 2020 and we identified one non-randomized study in OVID. There were no new non-indexed RCTs available.

Neutralizing Antibodies for Treatment

Section last reviewed and updated 3/3/2022

Last literature search conducted 1/31/2022

- Recommendation 21: Among ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab rather than no neutralizing antibody treatment. (Conditional recommendation, Moderate certainty of evidence)
  - Dosing for casirivimab/imdevimab is casirivimab 600 mg and imdevimab 600 mg IV. Subcutaneous injection is a reasonable alternative in patients for whom it cannot be given intravenously.
  - Dosing for sotrovimab is sotrovimab 500 IV once.
  - Dosing for bamlanivimab/etesevimab is bamlanivimab 700 mg and etesevimab 1400 mg IV.

  - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab.
  - Local variant susceptibility should be considered in the choice of the most appropriate neutralizing antibody therapy. Local availability of different monoclonal antibody combinations may be affected by predominance of local variants.
  - There are limited data on efficacy of bamlanivimab/etesevimab, casirivimab/imdevimab, or sotrovimab in high-risk patients under 18 years of age.
- Recommendation 22 (NEW 3/3/2022): In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel recommends bebtelovimab only in the context of a clinical trial. (Knowledge gap)
- Recommendation 23: Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)

Janus Kinase Inhibitors: Baricitinib

Section last reviewed and updated 10/11/2021

Last literature search conducted 9/30/2021

- Recommendation 24: Among hospitalized adults with severe* COVID-19 having elevated inflammatory markers, the IDSA panel suggests baricitinib rather than no baricitinib. (Conditional recommendation, Moderate certainty of evidence)
  - Baricitinib 4 mg per day (or appropriate renal dosing) up to 14 days or until discharge from hospital.
  - Baricitinib appears to demonstrate the most benefit in those with severe COVID-19 on high-flow oxygen/non-invasive ventilation at baseline.
  - Limited additional data suggest a mortality reduction even among patients requiring mechanical ventilation.
  - Patients who receive baricitinib for treatment of COVID-19 should not receive tocilizumab or other IL-6 inhibitors.
- Recommendation 25: Among hospitalized patients with severe* COVID-19 who cannot receive a corticosteroid (which is standard of care) because of a contraindication, the IDSA guideline panel suggests use of baricitinib with remdesivir rather than remdesivir alone. (Conditional recommendation, Low certainty of evidence)
  - Remark: Baricitinib 4 mg daily dose for 14 days or until hospital discharge. The benefits of baricitinib plus remdesivir for persons on mechanical ventilation are uncertain.

**Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation.*

Janus Kinase Inhibitors: Tofacitinib

Section last reviewed and updated 8/21/2021

Last literature search conducted 7/31/2021

- Recommendation 26: Among hospitalized adults with severe* COVID-19, but not on non-invasive or invasive mechanical ventilation, the IDSA panel suggests tofacitinib rather than no tofacitinib. (Conditional recommendation, Low certainty of evidence)
  - Tofacitinib appears to demonstrate the most benefit in those with severe COVID-19 on supplemental or high-flow oxygen.
  - Patients treated with tofacitinib should be on at least prophylactic dose anticoagulant.

- Patients who receive tofacitinib should not receive tocilizumab or other IL-6 inhibitor for treatment of COVID-19.
- The STOP-COVID Trial did not include immunocompromised patients.

**Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device.*

Ivermectin

Section last reviewed and updated 8/10/2021

Last literature search conducted 7/31/2021

- Recommendation 27: In hospitalized patients with COVID-19, the IDSA panel suggests against ivermectin outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)
- Recommendation 28: In ambulatory persons with COVID-19, the IDSA panel suggests against ivermectin outside of the context of a clinical trial. (Conditional recommendation, very low certainty of evidence)

Fluvoxamine

Section last reviewed and updated 11/8/2021

Last literature search conducted 10/31/2021

- Recommendation 29: Among ambulatory patients with COVID-19, the IDSA guideline panel recommends fluvoxamine only in the context of a clinical trial. (Knowledge gap)

Nirmatrelvir/Ritonavir

Section last reviewed and updated 12/29/2021

Last literature search conducted 12/28/2021

- Recommendation 30: In ambulatory patients with mild to moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests nirmatrelvir/ritonavir initiated within five days of symptom onset rather than no nirmatrelvir/ritonavir. (Conditional recommendation, Low certainty of evidence)
  - Patients' medications need to be screened for serious drug interactions (i.e., medication reconciliation). Patients on ritonavir- or cobicistat-containing HIV or HCV regimens should continue their treatment as indicated.
  - Dosing based on renal function:
    - Estimated glomerular filtration rate (eGFR) > 60 ml/min: 300 mg nirmatrelvir/100 ritonavir every 12 hours for five days
    - eGFR ≤60 and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
    - eGFR <30 mL/min: not recommended
  - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive nirmatrelvir/ritonavir

Molnupiravir

Section last reviewed and updated 12/28/2021

Last literature search conducted 12/28/2021

- Recommendation 31: In ambulatory patients (≥18 years) with mild to moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within five days of symptom onset rather than no molnupiravir. (Conditional recommendation, Low certainty of evidence)
  - Patients who put a higher value on the putative mutagenesis, adverse events or reproductive concerns, and a lower value on the uncertain benefits, would reasonably decline molnupiravir.
  - Molnupiravir 800 mg for five days.
  - Patients with mild to moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
  - Molnupiravir is not authorized under the FDA EUA for use in patients <18 years, because it may affect bone and cartilage growth.
  - Molnupiravir is not recommended under the FDA EUA for use during pregnancy.
  - Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19, because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

National COVID-19 Clinical Evidence Taskforce, 2022 [24].

Australian guidelines for the clinical care of people with COVID-19: version 51

Zielsetzung/Fragestellung

This guideline aims to provide specific, patient-focused recommendations on management and care of people with suspected or confirmed COVID-19. With the exception of chemoprophylaxis for the prevention of infection in people exposed to COVID -19, the guideline does not include other interventions used in the prevention of COVID-19 infection or transmission. Within each recommendation, the patient population of interest is specified.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: multidisciplinary guideline panels;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: All panel members complete a declaration of potential conflicts of interest, and absent themselves from discussions related to these potential conflicts;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Ständige Aktualisierung: Stand: 26.03.2022

LoE/GoR

- For systematic reviews, the risk of bias or quality assessment of included studies presented in the review is used where available. For individual primary studies, each study is assessed for risk of bias. Randomised trials are assessed using the Cochrane Risk of Bias 2.0 assessment tool. Non-randomised studies are assessed using the ROBINS-I Risk of Bias assessment tool.
- This guideline uses GRADE methodology, which is supported by the online guideline development and publication platform 'MAGICapp' (Making GRADE the Irresistible Choice)
- The following criteria are used in determining the strength of recommendations:
  - Strong for: moderate to high certainty evidence suggests that benefits in critical outcomes clearly outweigh the reported harms; a strong recommendation can be made in the absence of high-certainty evidence if patients are expected to highly desire such practice and there are no potential harms in providing it.
  - Strong against: moderate to high certainty evidence suggests harms outweigh benefits; high certainty evidence suggests lack of benefits.
  - Conditional for: moderate to high certainty evidence suggests equivalent benefits and harms, patients would mostly want to receive the practice, and there is no significant resources implication in doing so; low certainty evidencesuggests benefits outweigh harms and there are no significant implications in patients' preferences or resources implications.
  - Conditional against: moderate to high certainty evidence suggests equivalent benefits and harms, but there is expected large variation in patients' preference to receive this practice or important resource implications; low certainty evidence suggests harms outweigh benefits and there are no significant implications in patients' preferences or resource implications.
  - Consensus statement: evidence is absent or of insufficient certainty; unclearbalance between benefits and harms, and there is expected large variation in patients' preferences. No formal method of reaching consensus was used but this was addressed in internal reviews.

Recommendations

6. Disease-modifying treatments

6.1 Recommended disease-modifying treatments

6.1.1 Casirivimab plus imdevimab (Ronapreve)

6.1.1.1 Casirivimab plus imdevimab (Ronapreve) for adults

Conditional recommendation

Consider using casirivimab plus imdevimab within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Conditional recommendation

Consider using casirivimab plus imdevimab in **seronegative** adults hospitalised with moderate-to-critical COVID-19.

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** adults hospitalised with moderate-to-critical COVID-19.

6.1.1.2 Casirivimab plus imdevimab (Ronapreve) for pregnant or breastfeeding women

Conditional recommendation

Consider using casirivimab plus imdevimab within 7 days of symptom onset in pregnant or breastfeeding women with COVID-19 who do not require oxygen and have one or more risk factors for disease progression.

Conditional recommendation

Consider using casirivimab plus imdevimab in **seronegative** pregnant or breastfeeding women hospitalised with moderate to critical COVID-19.

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** pregnant or breastfeeding women who are hospitalised with moderate-to-critical COVID-19.

6.1.1.3 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab within 7 days of symptom onset in **children and adolescents with COVID-19 aged 12 years and over and weighing at least 40 kg who do not require oxygen** and who are at high risk of deterioration.

Only in research settings

Do not use casirivimab plus imdevimab in children under 12 years of age without risk factors for deterioration who have **mild or asymptomatic COVID-19** outside of randomised trials with appropriate ethical approval.

Consensus recommendation

Consider using, in exceptional circumstances, casirivimab plus imdevimab in **seronegative** children and adolescents aged 12 years and over and weighing at least 40 kg who require oxygen and who are at high risk of disease progression.

Not recommended

Do not use casirivimab plus imdevimab in **seropositive** children and adolescents hospitalised with moderate-to-critical COVID-19.

6.1.2 Corticosteroids (inhaled)

6.1.2.1 Corticosteroids (inhaled) for adults

Conditional recommendation

Consider using inhaled corticosteroids (budesonide or ciclesonide) within 14 days of symptom onset in adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

6.1.2.2 Corticosteroids (inhaled) for children and adolescents

Conditional recommendation

Consider using inhaled corticosteroids (budesonide and ciclesonide) within 14 days of symptom onset for the treatment of symptomatic COVID-19 in children and adolescents who do not require oxygen and who have one or more risk factors for disease progression.

6.1.3 Corticosteroids (systemic)

6.1.3.1 Corticosteroids (systemic) for adults

Recommended

Use intravenous or oral dexamethasone for up to 10 days (or acceptable alternative regimen) in **adults with COVID-19 who require oxygen** (including mechanically ventilated patients).

Conditional recommendation against

Do not routinely use dexamethasone (or other systemic corticosteroid) to treat COVID-19 in **adults who do not require oxygen**.

6.1.3.2 Corticosteroids (systemic) for pregnant or breastfeeding women

Recommended

Use dexamethasone 6mg intravenously or orally for up to 10 days in **pregnant or breastfeeding women with COVID-19 who require oxygen** (including mechanically ventilated patients).

If steroids are indicated for fetal lung maturity in women at risk of preterm birth, a standard antenatal corticosteroid regimen should be used (e.g. intramuscular dexamethasone 6mg every 12 hours for four doses), followed by 6mg dexamethasone daily until 10 days has been reached.

If steroids are not indicated for fetal lung maturity, use dexamethasone 6mg daily intravenously or orally for up to 10 days.

Conditional recommendation against

Do not routinely use dexamethasone (or other systemic corticosteroid) to treat COVID-19 in pregnant or breastfeeding women who do not require oxygen.

6.1.3.3 Corticosteroids (systemic) for children and adolescents

Conditional recommendation

Consider using dexamethasone daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in **children and adolescents with acute COVID-19 who require oxygen** (including mechanically ventilated patients).

Conditional recommendation against

Do not routinely use dexamethasone (or other oral or parenteral steroids) to treat COVID-19 in **children and adolescents who do not require oxygen**.

6.1.4 Molnupiravir (Lagevrio)

6.1.4.1 Molnupiravir (Lagevrio) for adults

Consensus recommendation

Consider using molnupiravir within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression, where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Within the patient population for which molnupiravir is recommended for use (see Remark), decisions about the appropriateness of treatment with molnupiravir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of molnupiravir is unclear in individuals who are up-to-date with vaccination or partially vaccinated. Additional recommendations for other patient groups are currently under development and will be included in a future version of the guideline.*

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using molnupiravir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunocompromised regardless of vaccination status; or
- who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors

AND where other treatments (such as sotrovimab or nirmatrelvir plus ritonavir) are not suitable or available.

Implications for research

Given the limited evidence of benefit or safety, small effect sizes and absence of evidence evaluating the effectiveness of molnupiravir for SARS-CoV-2 variants of concern, rigorous data collection should be undertaken on indications and key outcomes for patients who receive treatment with molnupiravir.

6.1.4.2 Molnupiravir (Lagevrio) for pregnant or breastfeeding women

Only in research settings

Do not use molnupiravir (Lagevrio) for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

6.1.4.3 Molnupiravir (Lagevrio) for children and adolescents

Only in research settings

Do not use molnupiravir (Lagevrio) for the treatment of COVID-19 in children and adolescents outside of randomised trials with appropriate ethical approval.

6.1.5 Nirmatrelvir plus ritonavir (Paxlovid)

6.1.5.1 Nirmatrelvir plus ritonavir (Paxlovid) for adults

Conditional recommendation

Consider using nirmatrelvir plus ritonavir (Paxlovid) within 5 days of symptom onset in unvaccinated adults* with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in individuals who are up-to-date with vaccination or partially vaccinated. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated patients or in immunocompromised patients regardless of vaccination status.*

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir (Paxlovid) within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunocompromised regardless of vaccination status; or
- who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors.

6.1.5.2 Nirmatrelvir plus ritonavir (Paxlovid) for pregnant or breastfeeding women

Only in research settings

Do not use nirmatrelvir plus ritonavir (Paxlovid) in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

6.1.5.3 Nirmatrelvir plus ritonavir (Paxlovid) for children and adolescents

Only in research settings

Do not use nirmatrelvir plus ritonavir (Paxlovid) in children and adolescents outside of randomised trials with appropriate ethical approval.

6.1.6 Other immunomodulating drugs

6.1.6.1 Baricitinib

6.1.6.1.1 Baricitinib for adults

Conditional recommendation

Consider using baricitinib in adults hospitalised with COVID-19 who require supplemental oxygen.

6.1.6.1.2 Baricitinib for pregnant or breastfeeding women

Only in research settings

Do not use baricitinib for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

6.1.6.1.3 Baricitinib for children and adolescents

Only in research settings

Do not use baricitinib for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

6.1.6.2 Sarilumab

6.1.6.2.1 Sarilumab for adults

Conditional recommendation

Consider using sarilumab for the treatment of COVID-19 in adults who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation.

6.1.6.2.2 Sarilumab for pregnant or breastfeeding women

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in pregnant or breastfeeding women outside randomised trials with appropriate ethical approval.

6.1.6.2.3 Sarilumab for children and adolescents

Only in research settings

Do not use sarilumab for the treatment of COVID-19 in children and adolescents outside randomised trials with appropriate ethical approval.

6.1.6.3 Tocilizumab

6.1.6.3.1 Tocilizumab for adults

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in adults who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

6.1.6.3.2 Tocilizumab for pregnant or breastfeeding women

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in pregnant or breastfeeding women who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

6.1.6.3.3 Tocilizumab for children and adolescents

Conditional recommendation

Consider using tocilizumab for the treatment of COVID-19 in children and adolescents who require supplemental oxygen, particularly where there is evidence of systemic inflammation.

6.1.7 Remdesivir

6.1.7.1 Remdesivir for adults

Conditional recommendation

Consider using remdesivir in adults with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

Not recommended

Do not start remdesivir in adults hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Conditional recommendation

Consider using remdesivir within 7 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which remdesivir is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with remdesivir should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* *Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of remdesivir is unclear in individuals who are up-to-date with vaccination or partially vaccinated. See consensus recommendation for guidance on use of remdesivir in vaccinated patients or in immunocompromised patients regardless of vaccination status.*

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using remdesivir within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunocompromised regardless of vaccination status; or
- who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors.

6.1.7.2 Remdesivir for pregnant or breastfeeding women

Conditional recommendation

Consider using remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require oxygen but do not require non-invasive or invasive ventilation.

Not recommended

Do not start remdesivir in pregnant or breastfeeding women hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Conditional recommendation New

Consider using remdesivir within 7 days of symptom onset in pregnant women with COVID-19 who do not require oxygen and who have one or more additional risk factors for disease progression.

Remark:
In adults with confirmed COVID-19 who do not require oxygen, remdesivir probably decreases the risk of hospitalisation if taken within 7 days of onset of symptoms.

Results are based on a single trial *[644]*, in which unvaccinated adults were administered three intravenous doses of remdesivir on consecutive days (200 mg on day 1, followed by 100 mg on days 2 and 3). Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- Age ≥ 60 years
- Diabetes
- Obesity (BMI ≥ 30 kg/m2)
- Chronic kidney disease (any stage)
- Cardiovascular or cerebrovascular disease (coronary artery disease, congenital heart disease, heart failure, cardiomyopathy or history of stroke)
- Hypertension (systemic or pulmonary)
- Chronic liver disease
- Chronic lung disease (chronic obstructive pulmonary disease, moderate-severe asthma, cystic or pulmonary fibrosis)
- Sickle cell disease
- Current cancer
- Immunocompromised state (no definition provided)

Pregnant and breastfeeding women were not included in the trial. Eight paediatric patients aged 12–18 years were included, none of whom progressed to hospitalisation or death.

The efficacy of remdesivir in vaccinated and immunocompromised patients is unknown.

This is a high priority recommendation and will be updated as soon as new evidence becomes available.

6.1.7.3 Remdesivir for children and adolescents

Conditional recommendation against

Do not routinely use remdesivir for the treatment of COVID-19 in children and adolescents who require oxygen.

Consensus recommendation New

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in **children and adolescents aged 12 years and over and weighing at least 40 kg** who do not require oxygen and who are at high risk of deterioration.

Consider using remdesivir only in children and adolescents who are not up-to-date with vaccination, or those who are immunosuppressed regardless of vaccination status. Do not routinely use remdesivir in children and adolescents who are up-to-date with vaccination unless immunosuppressed.

Decisions about the appropriateness of treatment with remdesivir should be based on the patient's individual risk of severe disease, on the basis of age or multiple risk factors, and COVID-19 vaccination status.

Only in research settings New

Do not use remdesivir for the treatment of COVID-19 in children under 12 years of age outside of randomised trials with appropriate ethical approval.

6.1.8 Sotrovimab

6.1.8.1 Sotrovimab for adults

Conditional recommendation

Consider using sotrovimab within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which sotrovimab is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with sotrovimab should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of sotrovimab is unclear in individuals who are up-to-date with vaccination or partially vaccinated. See consensus recommendation for guidance on use of sotrovimab in vaccinated patients or in immunocompromised patients regardless of vaccination status.*

Consensus recommendation

In addition to at-risk unvaccinated adults, also consider using sotrovimab within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunocompromised regardless of vaccination status; or
- who are not up-to-date with vaccination and who are at high risk of disease on the basis of age and multiple risk factors

6.1.8.2 Sotrovimab for pregnant women

Conditional recommendation

Consider using sotrovimab within 5 days of symptom onset in pregnant women with COVID-19 in the second or third trimester who do not require oxygen and who have one or more additional risk factors for disease progression.

Consensus recommendation

Within the population of pregnant women for whom sotrovimab is conditionally recommended for use (as listed above), decisions about the appropriateness of treatment with sotrovimab should be based on the patient's individual risk of severe disease, on the basis of multiple risk factors, and COVID-19 vaccination status.

Consider using sotrovimab in patients who are not up-to-date with vaccination and patients who are immunosuppressed regardless of vaccination status.

Do not routinely use sotrovimab in patients who are up-to-date with vaccination unless immunosuppressed.

6.1.8.3 Sotrovimab for children and adolescents

Consensus recommendation

Consider using, in exceptional circumstances, sotrovimab for the treatment of COVID-19 within 5 days of symptom onset in **children and adolescents aged 12 years and over and weighing at least 40 kg** who do not require oxygen and who are at high risk of deterioration.

Consider using sotrovimab only in children and adolescents who are not up-to-date with vaccination, or those who are immunosuppressed regardless of vaccination status. Do not routinely use sotrovimab in children and adolescents who are up-to-date with vaccination unless immunosuppressed.

Decisions about the appropriateness of treatment with sotrovimab should be based on the patient's individual risk of severe disease, on the basis of age or multiple risk factors, and COVID-19 vaccination status.

Only in research settings

Do not routinely use sotrovimab outside of randomised trials with appropriate ethical approval for the treatment of COVID-19 in children and adolescents under 12 years of age and without high risk factors for deterioration.

6.1.9 Tixagevimab plus cilgavimab (Evusheld)

6.1.9.1 Tixagevimab plus cilgavimab (Evusheld) for adults

Conditional recommendation New

Consider using tixagevimab plus cilgavimab (Evusheld) within 5 days of symptom onset in unvaccinated* adults with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression.

Within the patient population for which tixagevimab plus cilgavimab is conditionally recommended for use (see Remark), decisions about the appropriateness of treatment with tixagevimab plus cilgavimab should be based on the patient's individual risk of severe disease, on the basis of age and multiple risk factors, COVID-19 vaccination status and time since vaccination.

* *Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of tixagevimab plus cilgavimab is unclear in individuals who are up-to-date with vaccination or partially vaccinated. See consensus recommendation for guidance on use of tixagevimab plus cilgavimab in vaccinated patients or in immunocompromised patients regardless of vaccination status.*

Consensus recommendation New

In addition to at-risk unvaccinated adults, also consider using tixagevimab plus cilgavimab (Evusheld) within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and:

- are immunocompromised regardless of vaccination status; or
- who are not up-to-date with vaccination and who are at high risk of severe disease on the basis of age and multiple risk factors.

6.1.9.2 Tixagevimab plus cilgavimab (Evusheld) for pregnant or breastfeeding women

Only in research settings New

Do not use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19 in pregnant or breastfeeding women outside of randomised trials with appropriate ethical approval.

6.1.9.3 Tixagevimab plus cilgavimab (Evusheld) for children and adolescents

Consensus recommendation New

Consider using, in exceptional circumstances, tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19 within 5 days of symptom onset in **children and adolescents aged 12 years and over and weighing at least 40 kg** who do not require oxygen and who are at high risk of deterioration.

Consider using tixagevimab plus cilgavimab only in children and adolescents who are not up-to-date with vaccination, or those who are immunosuppressed regardless of vaccination status. Do not routinely use tixagevimab plus cilgavimab in fully vaccinated patients unless immunosuppressed.

Decisions about the appropriateness of treatment with tixagevimab plus cilgavimab should be based on the patient's individual risk of severe disease, on the basis of age or multiple risk factors, and COVID-19 vaccination status.

Only in research settings New

Do not use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19 in children under 12 years of age without risk factors for deterioration who do not require oxygen outside of randomised trials with appropriate ethical approval.

6.2 Disease-modifying treatments that are not recommended

- Aspirin
- Azithromycin
- Colchicine
- Convalescent plasma
- Hydroxychloroquine
- Hydroxychloroquine plus azithromycin
- Interferon beta-1a
- Interferon β-1a plus lopinavir-ritonavir

- Lopinavir-ritonavir

6.3 Disease-modifying treatments not recommended outside of clinical trials

- Dutasteride
- Angiotensin 2 receptor agonist (C21)
- Camostat mesylate
- Chloroquine
- Doxycycline
- Ivermectin
- Ivermectin plus doxycycline
- Nitazoxanide
- Telmisartan
- Sulodexide
- Baloxavir marboxil
- Darunavir-cobicistat
- Enisamium
- Favipiravir
- Sofosbuvir-daclatasvir
- Triazavirin
- Umifenovir
- Human umbilical cord mesenchymal stem cells
- Intravenous immunoglobulin
- Intravenous immunoglobulin plus methylprednisolone
- Anakinra
- Lenzilumab
- Ruxolitinib
- Tofacitinib
- Interferon beta-1a (inhaled)
- Interferon β-1b
- Interferon gamma
- Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2)
- Peginterferon lambda
- Bamlanivimab
- Bamlanivimab plus etesevimab
- Regdanvimab
- Aprepitant
- Bromhexine hydrochloride
- Fluvoxamine
- Metformin
- Recombinant human granulocyte colony-stimulating factor (rhG-CSF)

- Combined metabolic activators (CMA)
- N-acetylcysteine
- Vitamin C
- Vitamin D analogues (calcifediol/cholecalciferol)
- Zinc

WHO, 2022 [39,40].

World Health Organization (WHO)

Therapeutics and COVID-19: living guideline; WHO-2019-nCoV-therapeutics-2022.2

Living guidance for clinical management of COVID-19; WHO/2019-nCoV/clinical/2021.2

Zielsetzung/Fragestellung

What is the role of drugs in the treatment of patients with COVID-19?

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert

Recherche/Suchzeitraum:

- Living systematic review. Letzte Aktualisierung: 03.03.2022

LoE/GoR

- GRADE methodology

EMPFEHLUNGEN

6.1 Molnupiravir (published 3 March 2022)

For patients with non-severe COVID-19 (excluding pregnant and breastfeeding women, and children)

Conditional recommendation

New

We suggest treatment with molnupiravir, conditional to those at highest risk of hospitalization *(conditional recommendation for).*

- *In the absence of credible tools to predict risk for hospitalization in people infected with SARS-CoV-2, typical characteristics of people at highest risk include those that lack COVID-19 vaccination, with older age, immunosuppresion and/or chronic diseases (e.g. diabetes).*
- *The benefit will be trivial in absolute terms except in those at highest risk for hospitalization, for which the intervention should be reserved and given early on in disease.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with molnupiravir.*
- *The longer-term harms of molnupiravir remain unknown in the absence of clinical evidence, both for individual patients and at the population level. These include genotoxicity, emergence of resistance, and emergence of new variants (see Mechanism of Action).*
- *The conditional recommendation reflects the concern for widespread treatment with molnupiravir before more safety data become available.*
- *Use of molnupiravir should be accompanied by mitigation strategies such as avoiding the drug in younger adults, active pharmacovigilance programmes, and monitoring viral polymerase and spike sequences (see Justification).*
- *Alternative effective treatments with different safety profiles recommended by WHO, such as neutralizing monoclonal antibodies, like sotrovimab, may be preferable or antivirals (currently under WHO assessment) if available.*

6.2 Janus kinase inhibitors (published 14 January 2022)

Info Box

Recommendations concerning janus kinase (JAK) inhibitors, specifically baricitinib, ruxolitinib and tofacitinib, for patients with severe or critical COVID-19 were published on 14 January 2022 as the eighth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of three RCTs for baricitinib, two RCTs for ruxolitinib, and one RCT for tofacitinib, as per the LNMA on drug therapies *(3)*. No changes were made for the JAK inhibitors recommendations in this ninth version of the guideline.

Baricitinib, for patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with baricitinib *(strong recommendation for).*

- *Along with baricitinib, corticosteroids should also be administered in patients with severe or critical COVID-19 (see Section 6.11).*
- *IL-6 receptor blockers (tocilizumab or sarilumab) have previously been recommended for the treatment of patients with severe or critical COVID-19 (see Section 6.6). An IL-6 receptor blocker and baricitinib should not be given together, and should be viewed as alternatives. The choice of whether to use baricitinib or an IL-6 receptor blocker depends on availability, as well as clinical and contextual factors (see Justification).*

Ruxolitinib and tofacitinib, for patients with severe or critical COVID-19

Conditional recommendation against

We suggest not to use ruxolitinib or tofacitinib (*conditional recommendation against*).

- *Clinicians should consider using these drugs only if neither baricitinib nor IL-6 receptor blockers (tocilizumab or sarilumab) are available.*
- *The GDG emphasized the need for more trial evidence to better inform the recommendations.*

6.3 Sotrovimab (published 14 January 2022)

Info Box

Recommendations concerning sotrovimab for patients with non-severe COVID-19 were published on 14 January 2022 as the eighth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of one RCT for non-severe illness, as per the LNMA on antibody and cellular therapies (2). No changes were made for the sotrovimab recommendation in this ninth version of the guideline.

For patients with non-severe COVID-19

Conditional recommendation

We suggest treatment with sotrovimab, conditional to those at highest risk of hospitalization (*conditional recommendation for*).

- *Whereas sotrovimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial in absolute terms except in those at highest risk for hospitalization, for which the intervention should be reserved.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with sotrovimab.*
- *In the absence of credible tools to predict risk for hospitalization in people infected with COVID-19, typical characteristics of people at highest risk include those who are unvaccinated, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).*
- *Casirivimab-imdevimab were also conditionally recommended (see Section 6.5) and represent an alternative to sotrovimab; the two drugs should not be given together. The choice of which monoclonal antibodies to use depends on availability, as well as clinical and contextual factors, including emerging information about effectiveness with different variants (see Justification).*
- *Patients with severe or critical COVID-19: based on current evidence, the benefit of sotrovimab in seronegative patients with severe or critical COVID-19 (see casirivimab-imdevimab recommendation in Section 6.5) remains unclear. This means that careful clinical judgment needs to be applied if casirivimab-imdevimab is unavailable and sotrovimab is considered. New trial evidence for sotrovimab in this setting was published after the GDG developed recommendations for this iteration, and will be considered, alongside other publicly available emerging evidence, when developing future recommendations.*

6.4 Convalescent plasma (published 7 December 2021)

Info Box

Recommendations concerning convalescent plasma for patients with non-severe, severe and critical COVID-19 were published on 7 December 2021 as the seventh version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of 16 RCTs across disease severities, as per the LNMA on antibody and cellular therapies *(2)*. No changes were made for the convalescent plasma recommendations in this ninth version of the guideline.

For patients with non-severe COVID-19

Recommendation against

We recommend against treatment with convalescent plasma *(strong recommendation against)*.

6.5 Casirivimab-imdevimab (neutralizing monoclonal antibodies) (published 24 September 2021)

Info Box

Recommendations concerning neutralizing monoclonal antibodies (casirivimab-imdevimab) for patients with non-severe, severe or critical COVID-19 were published on 24 September 2021 as the sixth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It follows the availability of pre-prints of four trials, that are part of the larger adaptive randomized master protocol addressing patients with non-severe illness, and of the RECOVERY trial addressing severe and critically ill patients *(9)(10)(11)*. No changes were made for the casirivimab-imdevimab recommendations in this ninth version of the guideline.

Following the publication of a previous conditional recommendation for casirivimab-imdevimab, additional preclinical evidence has emerged (see Mechanism of action) *(76)*. There is a substantial body of pre-clinical in vitro data, and a confirmatory in vivo evaluation, demonstrating lack of efficacy of casirivimab-imdevimab against the Omicron BA1 variant (see Mechanism of action). As a result, casirivimab-imdevimab is no longer recommended for COVID-19 treatment except in cases where rapid viral genotyping is available and confirms infection with a SARS-CoV-2 variant (such as Delta) that is susceptible to the neutralizing activity of this combination of monoclonal antibodies.

For patients with non-severe COVID-19

Conditional recommendation

Updated

We suggest treatment with casirivimab-imdevimab, conditional to those at highest risk of hospitalization, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding Omicron BA1) *(conditional recommendation for)*.

- *Whereas casirivimab-imdevimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial in absolute terms for all but those at highest risk for which the intervention should be reserved.*
- *The panel identified a risk beyond 10% of being hospitalized for COVID-19 to represent a threshold at which most people would want to be treated with casirivimab-imdevimab.*
- *In the absence of credible tools to predict risk for hospitalization in people infected with COVID-19, typical characteristics of people at highest risk include lack of vaccination, older people, or those with immunodeficiencies and/or chronic diseases (e.g. diabetes).*

For patients with severe or critical COVID-19

Conditional recommendation

Updated

We suggest treatment with casirivimab-imdevimab, conditional to those with seronegative status, and where viral genotyping can confirm a susceptible SARS-CoV-2 variant (i.e. excluding omicron BA1) *(conditional recommendation for).*

- *With benefits of casirivimab-imdevimab observed only in patients with seronegative status, clinicians will need to identify these patients by credible tests available at the point of care to appropriately apply this recommendation (see Evidence to Decision section).*
- *Treatment with casirivimab-imdevimab is in addition to the current standard of care, which includes corticosteroids and IL-6 receptor blockers.*

6.6 IL-6 receptor blockers (published 6 July 2021)

Info Box

The recommendation concerning IL-6 receptor blockers (tocilizumab or sarilumab) was published on 6 July 2021 as the fifth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the publication of RECOVERY and REMAP-CAP trial publications in February 2021, and new trial data from 1020 patients randomized head-to-head to either tocilizumab or sarilumab in REMAP-CAP being made available to the WHO on 1 June 2021. No changes were made for the IL-6 receptor blocker recommendation in this ninth version of the guideline.

WHO has made a strong recommendation for JAK inhibitors, specifically baricitinib, in patients with severe and critical COVID-19. An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives. These new considerations are provided under 'Justification' for the recommendation for IL-6 receptor blockers, and are unchanged in this ninth version of the guideline.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) *(strong recommendation for).*

- *Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19 (see Section 6.11), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.*
- *Baricitinib, a JAK inhibitor, is now recommended for the treatment of patients with severe and critical COVID-19 (see Section 6.2). An IL-6 receptor blocker and baricitinib should not be given together and should be viewed as alternatives. The choice of whether to use baricitinib or an IL-6 receptor blocker depends on availability as well as clinical and contextual factors (see Justification).*

6.7 Ivermectin (published 31 March 2021)

Info Box

The recommendation concerning ivermectin was published on 31 March 2021 as the fourth version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the increased international attention on ivermectin as a potential therapeutic option.

No changes were made for the ivermectin recommendation in this ninth version of the guideline. We are aware of a few new, relatively small trials published since our recommendation was made and that one key trial has since been retracted given concerns about research fraud *(91)(92)*. However, the updated evidence summary from the LNMA is consistent with our previously made recommendation. This updated evidence summary will be fully considered by the GDG in subsequent iterations of the guideline.

For patients with COVID-19, regardless of disease severity

Only in research settings

We recommend not to use ivermectin, except in the context of a clinical trial *(recommended only in research settings).*

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

A recommendation to only use a drug in the setting of clinical trials is appropriate when there is very low certainty evidence and future research has a large potential for reducing uncertainty about the effects of the intervention and for doing so at reasonable cost.

6.8 Hydroxychloroquine (published 17 December 2020)

Info Box

The recommendation concerning hydroxychloroquine was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October, 2020, reporting results on treatment with hydroxychloroquine, remdesivir and lopinavir/ritonavir in hospitalized patients with COVID-19 *(15)*. No changes were made for the hydroxychloroquine recommendation in this ninth version of the guideline.

For patients with COVID-19, regardless of disease severity

Recommendation against

We recommend not to use hydroxychloroquine or chloroquine *(strong recommendation against).*

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

6.9 Lopinavir/ritonavir (published 17 December 2020)

Info Box

The recommendation concerning lopinavir/ritonavir was published 17 December 2020 as the third version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with lopinavir/ritonavirsivir, remdesivir and hydroxychloroquine in hospitalized patients with COVID-19 *(15)*. No changes were made for the lopinavir/ritonavir recommendation in this ninth version of the guideline.

For patients with COVID-19, regardless of disease severity

Recommendation against

We recommend not to use lopinavir/ritonavir *(strong recommendation against)*.

Remark: This recommendation applies to patients with any disease severity and any duration of symptoms.

https://apps.who.int/iris/bitstream/handle/10665/337876/WHO-2019-n
eng.pdf?sequence=1&isAllowed=y

6.10 Remdesivir (published 20 November 2020)

Info Box

The recommendation concerning remdesivir was published 20 November 2020 as the second version of the WHO living guideline and in the BMJ as Rapid Recommendations. It followed the pre-print publication of the WHO SOLIDARITY trial on 15 October 2020, reporting results on treatment with remdesivir, hydroxychloroquine and lopinavir/ritonavir in hospitalized patients with COVID-19 *(15)*. No changes were made for the remdesivir recommendation in this ninth version of the guideline. Of note, this recommendation is under review given new trials, and an update is planned in the next iteration of this guideline. The current recommendation provided is based on the initial assessment made by the GDG, and does not represent best current evidence.

For patients with COVID-19, regardless of disease severity

Conditional recommendation against

In review

We suggest not to use remdesivir *(conditional recommendation against)*.

6.11 Systemic corticosteroids (published 2 September 2020)

Info Box

The recommendations for corticosteroids were first published as WHO living guidelines 2 September 2020, and as BMJ Rapid Recommendations 5 September 2020. It followed the publication of the preliminary report of the RECOVERY trial, later published as a peer-reviewed paper *(14)*. No changes were made for the corticosteroids recommendations in this ninth version of the guideline.

Whereas the recommendations remain unchanged, the evidence summary for corticosteroids in patients with COVID-19 was updated before the sixth iteration of this living guideline. The baseline risk estimates for mortality are now based on the WHO SOLIDARITY trial (as for other drugs in this guideline) *(15)* rather than the initial ISARIC cohort study *(124)* that likely overestimates current mortality risks at the global level. The update was also needed to inform the baseline risk for mortality in the evidence summary informing the strong recommendation for IL-6 receptor blockers, in addition to standard of care for patients with severe or critical COVID-19, where corticosteroids provide a relative reduction in mortality by 21%.

For patients with severe or critical COVID-19

Strong recommendation for

We recommend treatment with systemic corticosteroids *(strong recommendation for)*.

For patients with non-severe COVID-19 infection

Conditional recommendation against

We suggest not to use systemic corticosteroids *(conditional recommendation against)*.

National Institute for Health and Care Excellence (NICE), 2022 [25].

COVID-19 rapid guideline: managing COVID-19; version 23.0

Zielsetzung/Fragestellung

This guideline is for health and care practitioners, and those involved in planning and delivering services. It provides guidance on managing COVID-19. The guideline makes recommendations about care in all settings for adults, children and young people with clinically diagnosed or laboratory-confirmed COVID-19.

- What investigations should be carried out, and when, to determine the appropriate management of COVID-19 and any complications?
- What is the clinical effectiveness and safety of pharmacological and non-pharmacological treatments for acute symptoms and complications of COVID-19?
- How should symptoms and complications be managed?
- How, and how often, should people with COVID-19 be followed up?
- What palliative and end-of-life strategies are effective for people with COVID-19?

Methodik

This guideline was developed using the methods and process in our interim process and methods for guidelines developed in response to health and social care emergencies.

We compiled a list of all recommendations in the COVID-19 rapid guidelines that were relevant to the scope of this guideline. These recommendations were added to the appropriate section in the draft structure of the new guideline. After NICE technical and clinical quality assurance of this mapping work, the recommendations were transferred to the relevant part of the structure on the publishing platform MAGICapp.

After the initial mapping, the structure was refined. The NICE expert advisory panel identified gaps in coverage and any recommendations that should be changed. The panel were also asked whether any of the recommendations from the rapid guidelines could be removed, if no longer relevant, due to new emergent evidence or due to recommendations being context specific and therefore bound to a particular time in the pandemic. Any changes to recommendation content were based on the consensus view of the expert advisory panel.

Grundlage der Leitlinie

- Repräsentatives Gremium: keine Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz:
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Living guidline: As there is a need for prompt guidance on therapeutics for managing COVID-19, NICE is collaborating with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for some recommendations.
- Letzte Aktualisierung: 30.03.2022

LoE/GoR

- GRADE

Sonstige methodische Hinweise

This guideline covers the management of COVID-19 for children, young people and adults in all care settings. It brings together our existing recommendations on managing COVID- 19 so that healthcare staff and those planning and delivering services can find and use them more easily. The guideline includes new recommendations on therapeutics, and we will update the guideline further as new evidence emerges.

EMPFEHLUNGEN

7 Therapeutics for COVID-19

7.1 Antivirals

7.1.1 Nirmatrelvir plus ritonavir

NICE is aware that new evidence is available for the combination of nirmatrelvir (also known as PF-07321332) plus ritonavir (Paxlovid) and will publish recommendations when this has been reviewed.

7.1.2 Remdesivir

- Conditional recommendation: Consider a 3-day course of remdesivir for adults, or young people aged 12 years and over who weigh at least 40 kg, with COVID-19 who:
  - do not need supplemental oxygen for COVID-19, and
  - are within 7 days of symptom onset, and
  - are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy provides a list of people who have been prioritised for treatment with antivirals.)
- Conditional recommendation: Consider a course of remdesivir (up to 5 days) for adults, or young people aged 12 years and over who weigh at least 40 kg, who:
  - have COVID-19 pneumonia, and
  - are in hospital and need low-flow supplemental oxygen.
- Only in research settings: Do not use remdesivir for COVID-19 pneumonia in adults, young people and children in hospital and on high-flow nasal oxygen, continuous positive airway pressure, non-invasive mechanical ventilation or invasive mechanical ventilation, except as part of a clinical trial.

7.1.3 Molnupiravir

- Conditional recommendation: Consider a 5-day course of molnupiravir for adults with COVID-19 who:
  - do not need supplemental oxygen for COVID-19, and
  - are within 5 days of symptom onset, and
  - are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy provides a list of people who have been prioritised for treatment with antivirals.)
- Not recommended: Do not offer molnupiravir to children and young people aged under 18, or pregnant women.

7.2 Neutralising monoclonal antibodies - for people not in hospital

- Recommended: Offer a neutralising monoclonal antibody for people aged 12 and over with COVID-19 who:
  - are not in hospital, and
  - are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy provides a list of people at high-risk prioritised for access to neutralising monoclonal antibodies).

7.3 Corticosteroids

- Recommended: Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:
  - need supplemental oxygen to meet their prescribed oxygen saturation levels or
  - have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

Continue corticosteroids for up to 10 days unless there is a clear indication to stop early, which includes discharge from hospital or a hospital-supervised virtual COVID ward.

- Conditional recommendation against: Do not routinely use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen, unless there is another medical indication to do so.

7.4 Casirivimab and imdevimab - for people hospitalised because of COVID-19

- Not recommended: New: Do not offer a combination of casirivimab and imdevimab to people hospitalised because of COVID-19 who are known or suspected to have infection caused by an Omicron variant (or any other variant not susceptible to casirivimab and imdevimab).
- Conditional recommendation: New: Only offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 when:
  - the infection is known to be caused by a variant susceptible to casirivimab and imdevimab, and
  - the person has no detectable SARS-CoV-2 antibodies (seronegative).

7.5 Tocilizumab

- Recommended: Offer tocilizumab to adults in hospital with COVID-19 if all the following apply:
  - they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
  - they have not had another interleukin-6 inhibitor during this admission
  - there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab.

  And they:
  - need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
  - are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.
- Only in research settings: Consider tocilizumab for children and young people who have severe COVID-19 or paediatric inflammatory multisystem syndrome only if they are 1 year and over, and only in the context of a clinical trial.

7.6 Sarilumab

- Conditional recommendation Consider sarilumab for COVID-19 in adults in hospital if tocilizumab is unavailable for this condition or cannot be used. Use the same eligibility criteria as those for tocilizumab. That is, if all the following apply:
  - they are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids
  - they have not had another interleukin-6 inhibitor during this admission

- there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by sarilumab.

And they:

- need supplemental oxygen and have a C-reactive protein level of 75 mg/litre or more, or
- are within 48 hours of starting high-flow nasal oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation.

7.9 Antibiotics

- Antibiotics should not be used for preventing or treating COVID-19 unless there is clinical suspicion of additional bacterial co-infection. See the section on suspected or confirmed co-infection.

7.10 Azithromycin

- Not recommended: Do not use azithromycin to treat COVID-19.

7.11 Budesonide (inhaled)

- Only in research settings: Only use budesonide to treat COVID-19 as part of a clinical trial.

7.12 Colchicine

- Not recommended: Do not use colchicine to treat COVID-19.

7.13 Doxycycline

- Not recommended: Do not use doxycycline to treat COVID-19 in the community.

7.14 Ivermectin

- Only in research settings: Do not use ivermectin to treat COVID-19 except as part of a clinical trial.

Chalmers JD et al., 2021 [7].

European Respiratory Society and endorsed by the Chinese Thoracic Society

Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline

Zielsetzung/Fragestellung

The objective of these guidelines is to provide evidence-based recommendations, primarily related to the management of hospitalised adults with COVID-19. This guideline does not address in detail the management of COVID-19 in the community, as the majority of evidence obtained relates to hospitalised patients. In addition, management in children is not addressed. A guideline cannot address the full complexity of a disease; hence, all recommendations should be interpreted considering the clinical circumstances and patients' perceptions, values and preferences.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: trifft zu;

Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: This work was funded by the European Respiratory Society.;

- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

The PubMed platform was used to search MEDLINE. EMBASE, International Clinical Trials Registry Platform (ICTRP) and CDC were also searched. The cut-off date for literature searches was 31 October 2020, with updates performed to identify key studies in November 2020 and again in February 2021.

LoE/GoR

- The panel selected outcomes of interest for each clinical question a priori, based on their relative importance to adult patients with COVID-19 and to clinical decision making (supplementary material).
- The importance of outcomes was rated on a 9-point scale (ranging from “not important” to “critical”) and only outcomes rated as important or critical for clinical decision making were included in the evidence tables.
- We followed the GRADE approach to assess the confidence in the evidence (quality) and the degree of recommendations. The GRADE methodology was used to rate the body of evidence at the outcome level rather than the study level, with assessment of risk of bias at study level performed as described [41]. One recommendation (on ventilatory support) was addressed using a narrative format due to the lack of homogeneous literature.
- The quality of evidence was rated on four levels (high, moderate, low or very low) based on the GRADE methodology [39].
- the panel formulated the clinical recommendations and decided on their strength by consensus, or, if required, by voting. Following the GRADE approach, strong recommendations are worded as “we recommend”, while conditional recommendations are worded as “we suggest”.

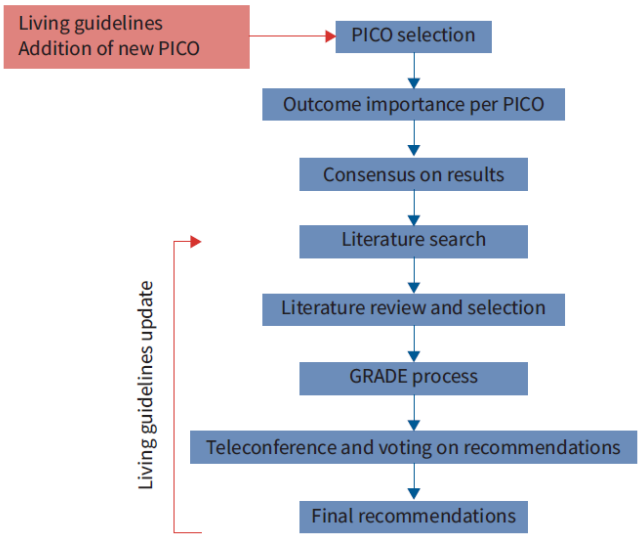


FIGURE 1 Process of guideline development. PICO: population, intervention, comparator, outcome.

Sonstige methodische Hinweise

This is a living guideline with the panel continuously reviewing new evidence as it arises. Recommendations for additional therapies not addressed in this guideline such as convalescent plasma, monoclonal antibodies directed against SARS-CoV-2 and other therapies will be added in future versions, along with updates on the therapies already reviewed once new data are available.

Empfehlungen

TABLE 2 Summary of recommendations in this guideline

Therapy	Recommendations	Strength of recommendation	Quality of Evidence
Corticosteroids	1) The panel recommends offering treatment with corticosteroids for patients with COVID-19 requiring oxygen, noninvasive ventilation or invasive mechanical ventilation	Strong	Moderate
	2) The panel recommends NOT to offer treatment with corticosteroids for patients with COVID-19 requiring hospitalisation but not requiring supplementary oxygen or ventilatory support	Strong	Moderate
IL-6 receptor antagonist monoclonal antibody	3) The panel suggests offering IL-6 receptor antagonist monoclonal antibody therapy to hospitalised patients with COVID-19 requiring oxygen or ventilatory support	Conditional	Low
	4) The panel suggests NOT to offer IL-6 receptor antagonist monoclonal antibody to patients not requiring supplementary oxygen	Conditional	Low
Hydroxychloroquine	5) The panel recommends NOT to offer hydroxychloroquine to patients with COVID-19, including hospitalised patients and outpatients	Strong	Moderate
Azithromycin	6) The panel suggests NOT to offer azithromycin to hospitalised patients with COVID-19 in the absence of bacterial infection	Conditional	Very low
Azithromycin and hydroxychloroquine	7) The panel suggests NOT to offer hydroxychloroquine and azithromycin in combination to patients with COVID-19	Conditional	Moderate
Colchicine	8) The panel suggests NOT to offer colchicine for hospitalised patients with COVID-19	Conditional	Very Low
Lopinavir–ritonavir	9) The panel recommends NOT to offer lopinavir–ritonavir to hospitalised patients with COVID-19	Strong	Low
Remdesivir	10) No recommendation is made regarding the use of remdesivir in patients hospitalised with COVID-19 and not requiring invasive mechanical ventilation	None	Moderate
	11) The panel suggests not to offer remdesivir to patients hospitalised with COVID-19 infection who require invasive mechanical ventilation	Conditional	Moderate
Interferon-β	12) The panel suggests NOT to offer interferon-β to hospitalised patients with COVID-19	Conditional	Very low
Anticoagulation	13) The panel recommends offering a form of anticoagulation to hospitalised patients with COVID-19	Strong	Very low
Noninvasive ventilatory support	14) We suggest HFNC or noninvasive CPAP delivered through either a helmet or a facemask for patients with COVID-19 and hypoxaemic acute respiratory failure without an immediate indication for invasive mechanical ventilation	Conditional	Very low

In the document, high-flow nasal cannula oxygen therapy (HFNC) is integrated in the term "noninvasive ventilatory support". IL: interleukin; COVID-19: coronavirus disease 2019; CPAP: continuous positive airway pressure.

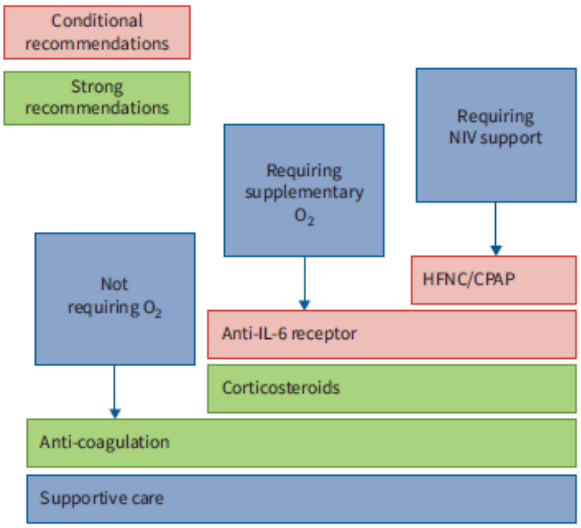


FIGURE 2 Summary of the European Respiratory Society guideline for management of hospitalised patients with coronavirus disease 2019. NIV: noninvasive ventilation; HFNC: high-flow nasal cannula oxygen; CPAP: continuous positive airway pressure; IL: interleukin.

Hintergrundinformationen:

PICO 2: In patients hospitalised with COVID-19, should IL-6 receptor antagonist monoclonal antibodies be used versus usual care (placebo or background therapy)?

Notes: 1) All patients eligible for IL-6 receptor antagonist monoclonal antibody treatment should have already received or should be receiving treatment with corticosteroids, unless contraindicated. 2) The patients most likely to benefit are: those in the first 24 h after receiving noninvasive or invasive ventilatory support; and those receiving supplementary oxygen and who are progressing despite corticosteroid treatment, or who are considered at high risk of future requirement for ventilatory support.

PICO 8: In patients hospitalised with COVID-19 should remdesivir be used versus standard of care (defined as no treatment, placebo or background therapy according to local practice)?

Recommendation

The panel makes **no recommendation** regarding the use of remdesivir in patients hospitalised with COVID-19 and not requiring invasive mechanical ventilation (no recommendation, moderate quality of evidence).

The panel suggests NOT to offer remdesivir to patients hospitalised with COVID-19 who require invasive mechanical ventilation (conditional recommendation, moderate quality of evidence).

Summary of evidence

Remdesivir is an inhibitor of the viral RNA-dependent RNA polymerase. It has proven effective in vitro against SARS-CoV-1, MERS-CoV and SARS-CoV-2 [93, 94]. A reduction in time to recovery and length of hospital stay was demonstrated for remdesivir in one trial (ACTT1) [95]. This trial randomised 1062 patients (541 to remdesivir and 521 to placebo) [95]. The primary outcome of recovery time was reduced from 15 days to 10 days (rate ratio for recovery 1.29, 95% CI 1.12–1.48; p<0.001). Length of hospital stay was also reduced from a median of 17 days to 12 days, and other secondary endpoints showed positive benefits [95]. In contrast, no clinical benefits were demonstrated in the other trials, including the large SOLIDARITY trial, which found no evidence of a mortality benefit. The SOLIDARITY analysis of remdesivir included 2743 receiving active treatment and 2708 controls. Mortality was not impacted, with a rate ratio of 0.95 (95% CI 0.81–1.11; p=0.50) [30]. The SOLIDARITY group also included an updated meta-analysis of existing trials including ACTT1, SOLIDARITY and additional trials that randomised patients 2:1, and concluded there was no mortality benefit of remdesivir (RR 0.91, 95% CI 0.79–1.05) [30]. Our review identified very similar results with an odds ratio for mortality of 0.92 (95% CI 0.79–1.07) with no increase in adverse events (OR 1.05, 95% CI 0.71–1.55) from three studies.

In ACTT1, no benefit on the primary outcome of clinical recovery (recovery rate ratio 0.98, 95% CI 0.70– 1.36) was observed in patients who started remdesivir when they were already on mechanical ventilation or extracorporeal membrane oxygenation [95]. If treatment is given it should be given for 5 days based on evidence that this is at least as effective as 10 days administration [96]. Liver function tests should be checked prior to administration of remdesivir and checked while patients are on treatment, remdesivir should not be prescribed in patients with severe renal dysfunction (GFR <30 mL·min−1).

Justification of the recommendation

The panel considers that time to recovery and length of hospital stay are relevant clinical endpoints in the absence of a mortality benefit of remdesivir. Nevertheless, these benefits have been demonstrated in only one randomised trial. The reported benefits are regarded by the panel as modest. The lack of significant adverse effects means that the balance of benefit versus risk was considered marginally in favour of the intervention by some members of the panel but not by others. The panel discussed this topic extensively, and voted on the final recommendation resulting in no majority favouring a recommendation for or a recommendation against remdesivir use. The panel therefore makes **no recommendation** regarding remdesivir in patients not requiring invasive mechanical ventilation. In GRADE methodology this **is referred to as a condition recommendation for the intervention OR the alternative**. This recommendation does not indicate that clinicians should use remdesivir routinely or that clinicians should avoid use of remdesivir in all cases. Rather it indicates that the balance of risks and benefits is uncertain and its use by patients should ideally be in the context of a randomised clinical study, or where patients have been fully informed of the risks and benefits.

Subgroup effects were observed with no benefit on the primary outcome evident in patients requiring invasive mechanical ventilation or extracorporeal membrane oxygenation. As this outcome is the main benefit supporting any use of remdesivir, the panel considers it appropriate to make a subgroup recommendation against remdesivir use in these patients where clear absence of benefit has been demonstrated. Availability and cost are important considerations for some healthcare systems.

Bassetti M et al., 2021 [5].

Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP)

Clinical management of adult patients with COVID-19 outside intensive care units

Zielsetzung/Fragestellung

For this reason, the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP) jointly developed the current guidelines for the therapeutic management of patients with COVID-19. The current document is relevant to patients not requiring (or still not requiring) admission to intensive care unit (ICU).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: kein Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert: A further update of the literature search will be performed in November 2021.

Recherche/Suchzeitraum:

- Ten different systematic reviews of the literature, one for each question.
- The initial search period was from inception of January 2020 to 30 November 2020, with two subsequent updates to 31 January 2021 and 30 April 2021.

LoE/GoR

- GRADE
- For observational studies, the risk of bias was assessed by means of the Newcastle–Ottawa Scale, whereas for RCTs the risk of bias was assessed by means of the Effective Practice and Organization of Care guidelines

Recommendation

Table 1 Summary of questions and recommendations

Question	Recommendations
Question 1	*When should a patient with COVID-19 be hospitalized?*
	Pending further evidence, it might be prudent not to base the decision to hospitalize or not patients with COVID-19 only on prognostic scores—*weak recommendation, very low certainty of evidence*
	Hospitalization should be considered in patients with at least one of the following: low oxygen saturation on room air ≤ 92% at rest or partial pressure of oxygen < 60 mmHg at arterial blood gas analysis*; respiratory rate > 30 breaths /min; new onset of dyspnea at rest or during speaking; reduction of oxygen saturation on room air below 90% during walking test; high value of prognostic scores; presence of anuria, confusion, hypotension, cyanosis, and/or other medical conditions requiring hospitalization per se—*best practice recommendation (based on expert opinion only)*
	*This does not strictly apply to patients with chronic obstructive pulmonary disease or other chronic respiratory disease, in whom similar values may be well tolerated, but who nonetheless need a careful personalized evaluation for hospitalization considering the presence of a baseline respiratory disease besides COVID-19
Question 2	*Which drugs should be administered to outpatients with COVID-19?*
	Based on available results from RCTs, we do not recommend the administration of hydroxychloroquine in outpatients with COVID-19—*strong recommendation, moderate certainty of evidence*
	We do not recommend the use of corticosteroids in outpatients with COVID-19, unless needed for other medical reasons—*best practice recommendation (based on expert opinion only)*
	In the absence of proven bacterial infections, the administration of antibiotics in outpatients with COVID-19 should be considered only as empirical treatment of highly suspected bacterial co-infection or superinfections—*weak recommendation, very low certainty of evidence (for azithromycin); best practice recommendation for other antibiotics (based on expert opinion only)*
	At the present time, antivirals should not be administered in outpatients with COVID-19 outside RCTs—*best practice recommendation (based on expert opinion only)*
	The use of neutralizing monoclonal antibodies may be considered in outpatients with COVID-19 with mild/moderate diseases at risk of progression and within at most 10 days after symptoms onset—*weak recommendation, low certainty of evidence*
	Of note, there was some agreement across the panel regarding the possibility to consider colchicine for the treatment of selected subgroups of outpatients with COVID-19, provided the favorable results in patients with positive COVID-19 molecular test in the COLCORONA RCT are replicated in other studies [66]

Question	Recommendations
Question 3	*Should anticoagulant agents be administered to inpatients with COVID-19?*
	Unless contraindicated, we recommend prophylactic anticoagulation in hospitalized patients with COVID-19—*strong recommendation, low certainty of evidence*
	Hospitalized patients with COVID-19 who were already under chronic anticoagulant therapy for well-defined indications, unless contraindicated, should continue anticoagulant treatment—*best practice recommendation (based on expert opinion only)*
	Therapeutic anticoagulation may be considered in patients possibly at higher risk of thrombotic events (serum d-dimer levels > 2.0 µg/mL) or with high suspicion for thrombotic complications—*best practice recommendation (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU

Question 4	*Should systemic steroids be administered to inpatients with COVID-19?*
	Unless contraindicated, we recommend the use of dexamethasone at the dosage of 6 mg/day for 10 days in inpatients with COVID-19 requiring oxygen supplementation*—*weak recommendation, low certainty of evidence*
	Methylprednisolone at the dosage of 0.5 mg/kg twice daily for at least 5 days could be considered in inpatients with COVID-19 requiring oxygen supplementation and aged 60 years or older—*weak recommendation, very low certainty of evidence*
	These recommendations are intended for inpatients with COVID-19 outside ICU
	*Equivalent dosages of other steroids may be considered if dexamethasone is not available (although this should be considered as best practice recommendation, taking also into account the indirectness of evidence for steroids other than dexamethasone)
Question 5	*Should antiviral agents be administered to inpatients with COVID-19?*
	Lopinavir/ritonavir should not be administered to hospitalized patients with COVID-19—*strong recommendation, moderate certainty of evidence*
	Pending further results from large RCTs, administration of a 5-day course of remdesivir should be considered in hospitalized patients with COVID-19 pneumonia requiring oxygen supplementation—*weak recommendation, very low certainty of evidence*
	Hydroxychloroquine should not be administered to hospitalized patients with COVID-19—*strong recommendation, moderate certainty of evidence*
	Other antiviral agents should not be administered for treating COVID-19 in hospitalized patients, unless they are administered within RCTs—*best practice recommendation (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU

Question	**Recommendations**
Question 6	*Should antibiotics be administered to inpatients with COVID-19?*
	We recommend against the routine use of antibiotics in hospitalized patients with COVID-19 without proven bacterial infection—*strong recommendation, moderate certainty of evidence (for azithromycin); weak recommendation, very low certainty of evidence (for antibiotics in general)*
	We recommend collection of respiratory specimens for culture or molecular detection of respiratory pathogens, blood cultures, and urinary antigens for *Streptococcus pneumoniae* and *Legionella* spp. in hospitalized patients with COVID-19 and suspected bacterial pneumonia—*best practice recommendation (based on expert opinion only)*
	Empirical antibiotic treatment of suspected bacterial pneumonia alongside proper diagnostic procedures, should be considered in patients with COVID-19 with evidence of consolidative radiological lesions—*best practice recommendation (based on expert opinion only)*
	In the case of empirical antibiotic treatment, selection of agents to be administered should follow standard practice for the treatment of bacterial pneumonia—*best practice recommendation (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU

Question 7	*Should neutralizing monoclonal antibodies and non-steroid immunomodulators be administered to inpatients with COVID-19?*
	Pending further results from RCTs, we recommend against the administration of neutralizing monoclonal antibodies in hospitalized patients with COVID-19—*strong recommendation, moderate certainty of evidence*
	We recommend considering tocilizumab administration in hospitalized patients with COVID-19 not responding to steroid treatment, with oxygen saturation < 92% on room air (including those already on supplementary oxygen), and with increased inflammatory markers* in the absence of a proven or suspected bacterial or fungal infection**—*weak recommendation, very low certainty of evidence*
	Pending further results from RCTs, baricitinib may be considered in addition to remdesivir in patients requiring high-flow oxygen or non-invasive mechanical ventilation who are not under steroid treatment (e.g., in the presence of contraindications to steroid use)—*weak recommendation, low certainty of evidence*
	Pending further results from large RCTs, we recommend against administration of other non-steroid immunomodulatory agents outside RCTs—*weak recommendation, very low certainty of evidence (for anakinra); best practice recommendation for other agents (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU
	*In the RECOVERY trial, serum C-reactive protein ≥ 75 mg/L
	**Clinicians should be aware of the following: (i) the 75 mg/L cutoff is based on results of the RECOVERY RCT; (ii) other markers of inflammation may be considered on a case-by-case basis (best practice recommendation); (iii) another best practice recommendation is to avoid tocilizumab administration in patients with severe immunosuppression or in those with other contraindications to tocilizumab administration (low platelet count; risk of gastrointestinal perforation; increase of transaminases > 5 times the upper limit of normal)
Question 8	*Should convalescent plasma be administered to inpatients with COVID-19?*
	Pending further results from RCTs, currently we do not support the administration of convalescent plasma in hospitalized patients with COVID-19 outside RCTs—*weak recommendation, low certainty of evidence*
	Pending further results from RCTs, currently we do not support the administration of anti-COVID-19 hyperimmune immunoglobulin preparations in hospitalized patients with COVID-19 outside RCTs—*best practice recommendation (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU
Question 9	*Should CPAP/NIV be employed for treating inpatients with COVID-19 with acute hypoxemic respiratory failure?*
	Unless contraindicated, non-invasive ventilatory support by means of NIV or CPAP is feasible and safe in patients with acute respiratory failure secondary to COVID-19, and should be considered for patients in whom standard oxygen supplementation is not or no longer sufficient and who do not require immediate intubation—*best practice recommendation (based on expert opinion only)*
	CPAP delivery systems allowing for PEEP titration should be preferred, and PEEP should not exceed 10 cmH_2O—*best practice recommendation (based on expert opinion only)*
	These recommendations are intended for inpatients with COVID-19 outside ICU
Question 10	*When can an improved patient with COVID-19 be discharged from an acute care hospital?*
	Clinically stable patients with COVID-19 who no longer require isolation (or who can be isolated outside the hospital) should be discharged from acute care hospitals when oxygen supplementation is no longer required or with a maximum requirement of low-flow oxygen at 2 L/min through nasal cannula (with the exception of patients already under oxygen supplementation at home at baseline or patients requiring initiation of long-term oxygen therapy after discharge), in line with common practice with other types of non-contagious lower respiratory tract infections, and provided there are no complications or other reasons that require continuation of hospitalization—*best practice recommendation (based on expert opinion only)*
	For patients with COVID-19 still requiring isolation but who could be discharged from a clinical standpoint, isolation outside the hospital (at home, in community facilities, or in long-term facilities, according to the specific need for non-acute care of any given patient) should be supported and made feasible for as many patients as possible—*best practice recommendation (based on expert opinion only)*

COVID-19 coronavirus disease 2019, *CPAP* continuous positive airway pressure, *NIV* non-invasive ventilation, *PEEP* positive end-expiratory pressure, *RCTs* randomized controlled trials

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 3 of 12, March 2022) am 07.03.2022

#	Suchfrage
1	[mh "COVID-19"]
2	[mh "SARS-CoV-2"]
3	[mh "Coronavirus Infections"]
4	(Covid* OR 2019ncov OR cov2 OR ncov19 OR sarscov* OR (ncov NEAR/3 2019) OR (ncov NEAR/3 19)):ti,ab,kw
5	(coronavir* OR (corona NEXT vir*) OR betacoronavir* OR (beta NEXT coronavir*) OR SARS*):ti,ab,kw
6	((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis)):ti,ab,kw
7	(wuhan AND (virus* OR viral OR viridae OR pneumonia* OR pneumonitis)):ti,ab,kw
8	("Severe Acute Respiratory Syndrome" OR "Severe Acute Respiratory Syndromes" OR "sudden acute respiratory syndrome" OR "severe acute respiratory infection" OR "severe acute respiratory infections" OR SARI):ti,ab,kw
9	{OR #1-#8}
10	#9 with Cochrane Library publication date Between Mar 2017 and Mar 2022

Systematic Reviews in PubMed am 07.03.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 02.01.2020.

#	Suchfrage
1	COVID-19/therapy[MeSH Terms]
2	COVID-19 drug treatment[Supplementary Concept] OR Coronavirus Infections/drug therapy[mh:noexp] OR Coronavirus Infections/therapy[mh:noexp]
3	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
4	Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov[ti] AND 2019[ti]) OR (ncov[ti] AND 19[ti])
5	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
6	(cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
8	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR

#	Suchfrage
	"severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (treatment*[ti] OR treating[ti] OR treated[ti] OR treat[ti] OR treats[ti] OR treatab*[ti] OR therapy[ti] OR therapies[ti] OR therapeutic*[ti] OR monotherap*[ti] OR polytherap*[ti] OR pharmacotherap*[ti] OR effect*[ti] OR efficacy[ti] OR management[ti] OR drug*[ti] OR intervent*[ti] OR (standard*[ti] AND care[ti]) OR antiviral*[ti] OR anti-viral*[ti] OR "Antiviral Agents"[mj] OR immunotherap*[ti] OR Immunotherapy[mj])
11	#1 OR #2 OR #10
12	(#11) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
13	(#12) AND ("2017/03/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT "The Cochrane database of systematic reviews"[Journal]

#	Suchfrage
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 07.03.2022

verwendete Suchfilter:
Konsentierter Standardfilter für Leitlinien (LL), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 21.06.2017.

#	Suchfrage
1	COVID-19/therapy[MeSH Terms]
2	COVID-19 drug treatment[Supplementary Concept] OR Coronavirus Infections/drug therapy[mh:noexp] OR Coronavirus Infections/therapy[mh:noexp]
3	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
4	Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov[ti] AND 2019[ti]) OR (ncov[ti] AND 19[ti])
5	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
6	(cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
8	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (treatment*[ti] OR treating[ti] OR treated[ti] OR treat[ti] OR treats[ti] OR treatab*[ti] OR therapy[ti] OR therapies[ti] OR therapeutic*[ti] OR monotherap*[ti] OR polytherap*[ti] OR pharmacotherap*[ti] OR effect*[ti] OR efficacy[ti] OR management[ti] OR drug*[ti] OR intervent*[ti] OR (standard*[ti] AND care[ti]) OR antiviral*[ti] OR anti-viral*[ti] OR "Antiviral Agents"[mj] OR immunotherap*[ti] OR Immunotherapy[mj])
11	#1 OR #2 OR #10
12	(#11) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp])
13	(#12) AND ("2017/03/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 01.04.2022

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- Leitlinienprogramm Onkologie (Deutsche Krebsgesellschaft, Deutsche Krebshilfe, AWMF)
- Nationale VersorgungsLeitlinien (NVL)

- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)

- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

1. **Abeldano Zuniga RA, Coca SM, Abeldano GF, Gonzalez-Villoria RAM.** Clinical effectiveness of drugs in hospitalized patients with COVID-19: a systematic review and meta-analysis. Ther Adv Respir Dis 2021;15:17534666211007214.
2. **Al-Abdouh A, Bizanti A, Barbarawi M, Jabri A, Kumar A, Fashanu OE, et al.** Remdesivir for the treatment of COVID-19: a systematic review and meta-analysis of randomized controlled trials. Contemp Clin Trials 2021;101:106272.
3. **Ansems K, Grundeis F, Dahms K, Mikolajewska A, Thieme V, Piechotta V, et al.** Remdesivir for the treatment of COVID-19. Cochrane Database of Systematic Reviews [online]. 2021(8):Cd014962. URL: http://dx.doi.org/10.1002/14651858.CD014962.
4. **Avni T, Leibovici L, Cohen I, Atamna A, Guz D, Paul M, et al.** Tocilizumab in the treatment of COVID-19: a meta-analysis. QJM 2021;114(8):577-586.
5. **Bassetti M, Giacobbe DR, Bruzzi P, Barisione E, Centanni S, Castaldo N, et al.** Clinical management of adult patients with COVID-19 outside intensive care units: guidelines from the Italian Society of Anti-Infective Therapy (SITA) and the Italian Society of Pulmonology (SIP). Infect Dis Ther 2021;10(4):1837-1885.
6. **Boppana TK, Mittal S, Madan K, Mohan A, Hadda V, Tiwari P, et al.** Steroid therapy for COVID-19: a systematic review and meta-analysis of randomized controlled trials. Monaldi Arch Chest Dis 2021;91(4).
7. **Chalmers JD, Crichton ML, Goeminne PC, Cao B, Humbert M, Shteinberg M, et al.** Management of hospitalised adults with coronavirus disease 2019 (COVID-19): a European Respiratory Society living guideline. Eur Respir J 2021;57(4):2100048.
8. **Chen CX, Hu F, Wei J, Yuan LT, Wen TM, Gale RP, et al.** Systematic review and meta-analysis of tocilizumab in persons with coronavirus disease-2019 (COVID-19). Leukemia 2021;35(6):1661-1670.
9. **Conti V, Corbi G, Sellitto C, Sabbatino F, Maci C, Bertini N, et al.** Effect of tocilizumab in reducing the mortality rate in COVID-19 patients: a systematic review with meta-analysis. J Pers Med 2021;11(7).
10. **Davidson M, Menon S, Chaimani A, Evrenoglou T, Ghosn L, Graña C, et al.** Interleukin-1 blocking agents for treating COVID-19. Cochrane Database of Systematic Reviews [online]. 2022(1):Cd015308. URL: http://dx.doi.org/10.1002/14651858.CD015308.
11. **Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM).** SARS-CoV-2/Covid-19-Informationen und Praxishilfen für niedergelassene Hausärztinnen und Hausärzte; S2e-Leitlinie, Version 22 [online]. AWMF-Registernummer 053-054. 04.02.2022. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2022. [Zugriff: 01.04.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/053-054l_S2e_SARS-CoV-2-Covid-19-Informationen-Praxishilfen-Hausaerztinnen-Hausaerzte_2022-02_2.pdf.
12. **Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin**

(DIVI), Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Deutsche Gesellschaft für Infektiologie (DGI). Empfehlungen zur stationären Therapie von Patienten mit COVID-19: Living Guideline; S3-Leitlinie, Version 7 [online]. AWMF-Registernummer 113-001LG. 01.03.2022. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2022. [Zugriff: 01.04.2022]. URL: https://www.awmf.org/uploads/tx_szleitlinien/113-001LGl_S3_Empfehlungen-zur-stationaeren-Therapie-von-Patienten-mit-COVID-19_2022-03.pdf.

13. **Ghosn L, Chaimani A, Evrenoglou T, Davidson M, Graña C, Schmucker C, et al.** Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database of Systematic Reviews [online]. 2021(3):Cd013881. URL: http://dx.doi.org/10.1002/14651858.CD013881.

14. **Gupta S, Padappayil RP, Bansal A, Daouk S, Brown B.** Tocilizumab in patients hospitalized with COVID-19 pneumonia: systematic review and meta-analysis of randomized controlled trials. J Investig Med 2022;70(1):55-60.

15. **Infectious Diseases Society of America (IDSA).** Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 8.0.0 [online]. 23.03.2022. Arlington (USA): IDSA; 2022. [Zugriff: 01.04.2022]. URL: https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v8.0.0.pdf.

16. **Juul S, Nielsen EE, Feinberg J, Siddiqui F, Jorgensen CK, Barot E, et al.** Interventions for treatment of COVID-19: second edition of a living systematic review with meta-analyses and trial sequential analyses (The LIVING Project). PLoS One 2021;16(3):e0248132.

17. **Kaka AS, MacDonald R, Greer N, Vela K, Duan-Porter W, Obley A, et al.** Major update: remdesivir for adults with COVID-19 : a living systematic review and meta-analysis for the American College of Physicians Practice Points. Ann Intern Med 2021;174(5):663-672.

18. **Kow CS, Hasan SS.** The effect of tocilizumab on mortality in hospitalized patients with COVID-19: a meta-analysis of randomized controlled trials. Eur J Clin Pharmacol 2021;77(8):1089-1094.

19. **Kreuzberger N, Hirsch C, Chai KL, Tomlinson E, Khosravi Z, Popp M, et al.** SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. Cochrane Database of Systematic Reviews [online]. 2021(9):Cd013825. URL: http://dx.doi.org/10.1002/14651858.CD013825.pub2.

20. **Kyriakopoulos C, Ntritsos G, Gogali A, Milionis H, Evangelou E, Kostikas K.** Tocilizumab administration for the treatment of hospitalized patients with COVID-19: a systematic review and meta-analysis. Respirology 2021;26(11):1027-1040.

21. **Li H, Yan B, Gao R, Ren J, Yang J.** Effectiveness of corticosteroids to treat severe COVID-19: a systematic review and meta-analysis of prospective studies. Int Immunopharmacol 2021;100:108121.

22. **Lin WT, Hung SH, Lai CC, Wang CY, Chen CH.** The effect of tocilizumab on COVID-19 patient mortality: a systematic review and meta-analysis of randomized controlled trials. Int Immunopharmacol 2021;96:107602.

23. **Malgie J, Schoones JW, Zeegers MP, Pijls BG.** Decreased mortality and increased side effects in COVID-19 patients treated with IL-6 receptor antagonists: systematic review and meta-analysis. Sci Rep 2021;11(1):21522.

24. **National COVID-19 Clinical Evidence Taskforce.** Australian guidelines for the clinical care of people with COVID-19: version 54.0 [online]. 26.03.2022. Melbourne (AUS): National COVID-19 Clinical Evidence Taskforce; 2022. [Zugriff: 01.04.2022]. URL: https://files.magicapp.org/guideline/17ccd08e-f908-45f3-acd3-25a3794e260d/published_guideline_6202-54_0.pdf.

25. **National Institute for Health and Care Excellence (NICE).** COVID-19 rapid guideline: managing COVID-19; version 23.0 [online]. 30.03.2022. London (GBR): NICE; 2022. [Zugriff: 01.04.2022]. (NICE guideline; Band 191). URL: https://www.nice.org.uk/guidance/ng191/resources/covid19-rapid-guideline-managing-covid19-pdf-51035553326.

26. **Ngamprasertchai T, Kajeekul R, Sivakorn C, Ruenroegnboon N, Luvira V, Siripoon T, et al.** Efficacy and safety of immunomodulators in patients with COVID-19: a systematic review and network meta-analysis of randomized controlled trials. Infect Dis Ther 2022;11(1):231-248.

27. **Okoli GN, Rabbani R, Copstein L, Al-Juboori A, Askin N, Abou-Setta AM.** Remdesivir for coronavirus disease 2019 (COVID-19): a systematic review with meta-analysis and trial sequential analysis of randomized controlled trials. Infect Dis (Lond) 2021;53(9):691-699.

28. **Selvaraj V, Khan MS, Bavishi C, Dapaah-Afriyie K, Finn A, Lal A, et al.** Tocilizumab in hospitalized patients with COVID-19: a meta analysis of randomized controlled trials. Lung 2021;199(3):239-248.

29. **Shankar-Hari M, Vale CL, Godolphin PJ, Fisher D, Higgins JPT, Spiga F, et al.** Association between administration of IL-6 antagonists and mortality among patients hospitalized for COVID-19: a meta-analysis. Jama 2021;326(6):499-518.

30. **Siemieniuk RA, Bartoszko JJ, Ge L, Zeraatkar D, Izcovich A, Kum E, et al.** Drug treatments for covid-19: living systematic review and network meta-analysis. BMJ 2020;370:m2980.

31. **Singh S, Khera D, Chugh A, Khera PS, Chugh VK.** Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis. BMJ Open 2021;11(6):e048416.

32. **Snow TAC, Saleem N, Ambler G, Nastouli E, Singer M, Arulkumaran N.** Tocilizumab in COVID-19: a meta-analysis, trial sequential analysis, and meta-regression of randomized-controlled trials. Intensive Care Med 2021;47(6):641-652.

33. **Sterne JAC, Murthy S, Diaz JV, Slutsky AS, Villar J, Angus DC, et al.** Association between administration of systemic corticosteroids and mortality among critically ill patients with COVID-19: a meta-analysis. JAMA 2020;324(13):1330-1341.

34. **Tanni SE, Silvinato A, Floriano I, Bacha HA, Barbosa AN, Bernardo WM.** Use of remdesivir in patients with COVID-19: a systematic review and meta-analysis. J Bras Pneumol 2022;48(1):e20210393.

35. **Tleyjeh IM, Kashour Z, Riaz M, Hassett L, Veiga VC, Kashour T.** Efficacy and safety of tocilizumab in COVID-19 patients: a living systematic review and meta-analysis, first update. Clin Microbiol Infect 2021;27(8):1076-1082.

36. **Tu J, Mo X, Zhang X, Xun J, Chen X, Liu Y, et al.** Effects of different corticosteroid therapy on severe COVID-19 patients: a meta-analysis of randomized controlled trials. Expert Rev Respir Med 2022;16(1):79-89.

37. **Vela D, Vela-Gaxha Z, Rexhepi M, Olloni R, Hyseni V, Nallbani R.** Efficacy and safety of tocilizumab versus standard care/placebo in patients with COVID-19: a systematic review and meta-analysis of randomized clinical trials. Br J Clin Pharmacol 2021 [Epub ahead of print].

38. **Verdugo-Paiva F, Acuña MP, Solá I, Rada G.** Remdesivir for the treatment of COVID-19: a living systematic review. Medwave 2020;20(11):e8080.

39. **World Health Organization (WHO).** Living guidance for clinical management of COVID-19; WHO/2019-nCoV/clinical/2021.2 [online]. 23.11.2021. Genf (SUI): WHO; 2021. [Zugriff: 01.04.2022]. URL: https://apps.who.int/iris/rest/bitstreams/1394399/retrieve.

40. **World Health Organization (WHO).** Therapeutics and COVID-19: living guideline; WHO-2019-nCoV-therapeutics-2022.2 [online]. 03.03.2022. Genf (SUI): WHO; 2022. [Zugriff: 01.04.2022]. URL: https://apps.who.int/iris/rest/bitstreams/1412704/retrieve.

41. **Zhang C, Jin H, Wen YF, Yin G.** Efficacy of COVID-19 treatments: a Bayesian network meta-analysis of randomized controlled trials. Front Public Health 2021;9:729559.

42. **Zhang J, Chen C, Yang Y, Yang J.** Effectiveness of tocilizumab in the treatment of hospitalized adults COVID-19: a systematic review and meta-analysis. Medicine (Baltimore) 2022;101(9):e28967.

[A] **Rethlefsen ML, Kirtley S, Waffenschmidt S, Ayala AP, Moher D, Page MJ, et al.** PRISMA-S: an extension to the PRISMA Statement for Reporting Literature Searches in Systematic Reviews. Syst Rev 2021;10(1):39. https://doi.org/10.1186/s13643-020-01542-z

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.021