Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2022-B-004-z Remdesivir

Stand: Januar 2022

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

Remdesivir
Behandlung von Erwachsenen mit 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.
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:	
Remdesivir J05AB16 Veklury®	Anwendungsgebiet laut Zulassung: 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.
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.
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.
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.
Sotrovimab N/N 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: 2022-B-004-z Remdesivir

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	05. November 2021

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
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 bei Erwachsenen

Hinweis zur Synopse:

- 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 *SARS-CoV-2-Infektion (COVID-19)* durchgeführt. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, SIGN, TRIP, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien.

Die Erstrecherche wurde am 09.02.2021 durchgeführt, die Folgerecherche am 12.08.2021. Die Folgerecherche nach aktuellen Versionen der Living Guidelines wurde am 03.11.2021 durchgeführt. Die Recherchestrategie der Erstrecherche wurde für die Folgerecherche übernommen und der Suchzeitraum jeweils auf die letzten 5 Jahre eingeschränkt. Die letzte Suchstrategie ist am Ende der Synopse detailliert dargestellt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 3444 Referenzen. 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 Quellen 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 20 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[l]	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.

3.2 Systematische Reviews

Singh S et al., 2021 [12].

Efficacy and safety of remdesivir in COVID-19 caused by SARS-CoV-2: a systematic review and meta-analysis

Fragestellung

Evaluation of remdesivir, an RNA polymerase inhibitor, for effectiveness in adults with COVID-19.

Methodik

Population:

- adults with COVID-19

Intervention vs. Komparator:

- Remdesivir vs. standard of care

Endpunkte:

- Primary objective: assessment of mortality (defined as deaths in each group).
- Secondary outcomes: clinical improvement and virological cure, serious adverse events (AEs) and other safety parameters.

Recherche/Suchzeitraum:

- Electronic literature search was performed in PubMed, Cochrane Central Register of Controlled Trials, in addition to clinicaltrials. gov on 20 September 2020, to identify the relevant published articles. Additional search was done in November 2020 for results of completed trials.

Qualitätsbewertung der Studien:

- ROB-2, GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 4 RCTs (n=7324 patients)

Charakteristika der Population:

Table 1 Characteristics of clinical studies evaluating remdesivir for treatment of COVID-19

Author, year (study design)	Institution/country of study conduct	Study interventions (N)/regimen	Study control (N)/regimen	Study population characteristics	Study outcomes
Beigel *et al* 2020 (randomised controlled trial)	Multicentre trial	Remdesivir (538); 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Placebo (521)	Hospitalised adults patients with COVID-19 with evidence of lower respiratory tract involvement.	**Time to recovery:** Patients in the remdesivir group had a shorter time to recovery than patients in the placebo group (median, 11 days, as compared with 15 days; rate ratio for recovery, 1.32; 95% CI (CI), 1.12 to 1.55; p<0.001 **Mortality:** Kaplan-Meier estimates of mortality by 14 days were 7.1% with remdesivir and 11.9% with placebo (HR for death, 0.70; 95% CI, 0.47 to 1.04)
Spinner *et al* (randomised controlled trial)	Multicentre trial	Remdesivir - 10 days (n=197), Remdesivir - 5 days (n=199)	Standard care (n=200)	Confirmed SARS-CoV-2 infection and moderate COVID-19 pneumonia (pulmonary infiltrates and room-air oxygen saturation >94%)	**Day 28** Mortality rate n(%) – remdesivir 10 day=3 (2); remdesivir 5 days=2 (1), standard=4 (2) Clinical Improvement n(%) - remdesivir 10 day=174((90), remdesivir 5 day=171(90), Standard=166(83)
Wang *et al* 2020 (randomised controlled trial)	Department of Pulmonary and Critical Care Medicine, China-Japan Friendship Hospital, Beijing, China	Remdesivir (158); at least 1 dose after entering ICU; 200 mg on day 1 followed by 100 mg on days 2–10 in single daily infusions	Placebo (79)	Hospitalised adults patients with COVID-19 symptom onset to enrolment interval of ≤12 days, oxygen saturation ≤94% on room air or a ratio of arterial oxygen partial pressure to fractional inspired oxygen of 300 mm Hg or less, and radiologically confirmed pneumonia	**Time to clinical improvement within 28 days after randomisation:** Remdesivir use was not associated with a difference in time to clinical improvement (HR 1.23 (95% CI 0.87 to 1.75)). Although not statistically significant, patients receiving remdesivir had a numerically faster time to clinical improvement than those receiving placebo among patients with symptom duration of 10 days or less (HR 1.52 (0.95 to 2.43) **28-day mortality:** similar between the two groups (22(14%] died in the remdesivir group vs 10 (13%) in the placebo group; difference 1.1% (95% CI –8.1 to 10.3)).
WHO Solidarity Trial 2020 (randomised controlled trial)	WHO, Multicentric trial (405 hospitals in 30 countries)	Remdesivir (2743); day 0, 200 mg; days 1–9, 100 mg	Placebo (2708)	Hospitalised with a diagnosis of COVID-19, age ≥18 years, not known to have received any study drug, without anticipated transfer elsewhere within 72 hours	**Mortality rate:** Remdesivir RR=0.95 (0.81 to 1.11, p=0.50; 301/2743 active vs 303/2708 control). Hydroxychloroquine RR=1.19 (0.89 to 1.59, p=0.23; 104/947 vs 84/906), Lopinavir RR=1.00 (0.79 to 1.25, p=0.97; 148/1399 vs 146/1372) Interferon RR=1.16 (0.96 to 1.39, p=0.11; 243/2050 vs 216/2050)

Qualität der Studien:

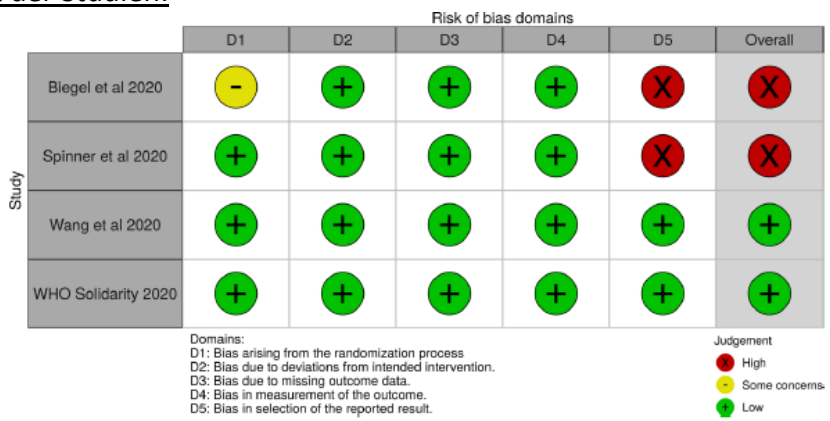


Figure 2 ROB-2: risk of bias in RCT evaluating remdesivir for treatment of COVID-19.

Studienergebnisse:

Table 2 GRADE recommendation for primary and secondary outcomes of use of remdesivir in COVID-19

Certainty assessment						No of patients		Effect		
No of studies Study design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Efficacy and safety of remdesivir	Placebo	Relative (95% CI)	Absolute (95% CI)	Certainty Importance
Mortality at day 28										
4 RCT	Not serious*	Not serious	Not serious	Serious†	None	387/3818 (10.1%)	394/3506 (11.2%)	**OR 0.92** (0.79 to 1.07)	**8 fewer per 1000** (from 21 fewer to 7 more)	⊕⊕⊕◯ moderate critical
Clinical improvement										
3 RCT	Serious‡	Not serious	Not serious	Serious§	None	782/1080 (72.4%)	484/799 (60.6%)	**OR 1.52** (1.24 to 1.87)	**94 more per 1000** (from 50 more to 136 more)	⊕⊕◯◯ low important
Time to clinical Improvement										
2 RCT	Serious¶	Not serious	Serious**	Serious§	None	-/0	-/0	**HR 1.28** (1.12 to 1.46)	**1 fewer per 1000** (from 1 fewer to 1 fewer)	⊕◯◯◯ very low important
Serious adverse events										
3 RCT	Serious‡	Not serious	Not serious	Serious§	None	161/1075 (15.0%)	179/800 (22.4%)	**RR 0.75** (0.62 to 0.90)	**56 fewer per 1000** (from 85 fewer to 22 fewer)	⊕⊕◯◯ low important
Respiratory failure										
2 RCT	Serious¶	Serious††	Not serious	Serious‡‡	None	44/691 (6.4%)	48/600 (8.0%)	**RR 0.85** (0.41 to 1.77)	**12 fewer per 1000** (from 47 fewer to 62 more)	⊕◯◯◯ very low critical

*All studies have low ROB except Biegel and Spinner *et al*. WHO solidarity trial contributing 77.9% wt to overall effect has low ROB. Hence overall low ROB.
†Overall information size of 1213 was achieved in either group. However, the overall effect estimate included one, hence downgraded for imprecision.
‡Biegel *et al* and Spinner *et al* have a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.
§Overall information size of 1213 was not achieved in either groups. Hence, downgraded for imprecision.
¶Biegel *et al* has a high risk of bias (ROB) due to selective reporting of results. Hence, downgraded for ROB.
**Time to clinical improvement is not a direct estimate of the patient's oriented outcomes. Hence, downgraded for evidence.
††As I^2 >50%, heterogeneity is significantly high. Hence, downgraded for inconsistency.
‡‡Overall information size of 1213 was not achieved in either group and the overall effect estimate included one, hence downgraded for imprecision.
RCT, randomised controlled trials; RR, risk ratio.

- Subgroup analysis revealed no mortality benefit in low-risk (no O2)(OR: 0,84, 95%CI: 0,41-1,75) and high-risk groups (O2 or assisted ventilation)(OR: 0,91, 95%CI: 0,73-1,13).

Anmerkung/Fazit der Autoren

Evidence of our systematic review indicates no benefit in mortality rate with remdesivir, with moderate quality of evidence. Benefit does exist in terms of rates of clinical improvement and faster time to clinical improvement in favour of remdesivir, but the evidence is of low and very low quality, respectively. Significant decrease in serious AEs as compared with placebo strengthens the evidence of more serious patients in placebo arm. No difference was shown in respiratory failure in the two groups (very low quality evidence). All outcomes except mortality in our meta-analysis were influenced by Beigel et al and Spinner et al, which has high ROB. WHO solidarity trial and Wang et al showed no mortality benefit, both having overall low ROB.

Kommentare zum Review

- Siehe auch: Al-Abdouh A et al., 2021 [2], De Cresenzo et al., 2021 [6], Okoli et al., 2021 [15], Juul et al., 2021 [10] und Kaka et al., 2021 [11].

Ma S et al., 2021 [18].

Efficacy and safety of systematic corticosteroids among severe COVID-19 patients: a systematic review and meta-analysis of randomized controlled trials

Fragestellung

to identify randomized controlled trials (RCTs) that evaluated corticosteroids in severe COVID-19 patients.

Methodik

Population:

- only severe COVID-19 patients (adults)

Intervention vs. Komparator:

- corticosteroids in combination with standard, usual care, compared with standard, usual care, or placebo alone, without corticosteroids

Endpunkte:

- The primary outcome was all-cause mortality at the longest follow-up, defined by the individual trial. The secondary outcomes included a composite disease progression and the incidence of serious adverse events during treatment.

Recherche/Suchzeitraum:

- Eligible RCTs were identified with a comprehensive systematic search of databases including PubMed, Embase, and Cochrane Central Register of Controlled Trials, from December 31, 2019 to October 1, 2020.

Qualitätsbewertung der Studien:

- Cochrane risk of bias tool, GRADE

Ergebnisse

Anzahl eingeschlossener Studien:

- 7 RCTs (n = 6250 patients)

Charakteristika der Population:

Table 1. Characteristics of included trials

Trial	Region of trial	Trial type	Inclusion criteria	Timing of corticosteroids	Dosage and duration of corticosteroids (*n*)	Control intervention (*n*)	Primary outcome in each trial	Longest follow-up
Angus et al.[3] REMAP-CAP	Australia, Canada, France, Ireland, the Netherlands, New Zealand, the UK, the USA	Multicenter, open-label, RCT	Aged at least 18 years Confirmed or suspected COVID-19 Admitted to ICU receiving respiratory or cardiovascular support	Given at study day 1 [1–4]	A fixed 7-day course of intravenous hydrocortisone (50 or 100 mg every 6 h) ($n = 137$)[a] OR A shock-dependent course (50 mg every 6 h up to 28 d for shock patients) ($n = 141$)	Usual care, no hydrocortisone ($n = 101$)	Respiratory and cardiovascular organ support-free days to 21 d	21 d
Corral et al.[15] GLUCOCOVID	Spain	Multicenter, partial randomized, preference, open-label controlled trial	Aged at least 18 years Confirmed COVID-19 Severe pneumonia, not intubated or	Not specified	Methylprednisolone 80 mg/d for 3 d, then 40 mg/d for 3 d ($n = 49$)[b]	Standard of care, no corticosteroids ($n = 29$)	A composite of death, ICU admission, or requirement of noninvasive ventilation	Until composite endpoint happened

Table 1. continued

Trial	Region of trial	Trial type	Inclusion criteria	Timing of corticosteroids	Dosage and duration of corticosteroids (*n*)	Control intervention (*n*)	Primary outcome in each trial	Longest follow-up
Dequin et al.[4] CAPE COVID	France	Multicenter, RCT	Aged at least 18 years Confirmed or suspected COVID-19 Admitted to ICU with acute respiratory failure	Within 24 h of the onset of the first severity criterion or within 48 h for patients referred from another hospital	Hydrocortisone 200 mg/d for 7 d, then 100 mg/d for 4 d and 50 mg/d for 3 d; if symptoms improved by day 4, then followed with hydrocortisone 100 mg/d for 2 d and 50mg/d for 2 d (*n* = 76)	Standard care (*n* = 73)	Death or persistent respiratory support on 21 d	21 d
Edalatifard et al.[15]	Iran	Multicenter, single-blind, RCT	Aged at least 18 years Confirmed COVID-19 Receiving oxygen therapy but not intubation or ventilation	Not specified	Methylprednisolone 250 mg/d for 3 d (*n* = 34)	Standard care (*n* = 28)[b]	Time to clinical improvement and hospital discharge or death	Until clinical improvement and hospital discharge or death
Horby et al.[2] RECOVERY	UK	Multicenter, open-label, RCT	Confirmed or suspected COVID-19 Received respiratory support[c]	Not specified	Oral or intravenous dexamethasone 6 mg/d for up to 10 d (or until hospital discharge if sooner) (*n* = 1603)	Usual care (*n* = 3287)	All-cause mortality within 28 d after randomization	28 d
Jeronimo et al.[17] Metcovid	Brazil	Single center, RCT	Aged at least 18 years Confirmed or suspected COVID-19 In use of oxygen therapy or under invasive mechanical ventilation	Not specified	Methylprednisolone 1 mg/kg/d for 5 d (*n* = 194)	Placebo (*n* = 199)	Mortality at 28 d	28 d
Tomazini et al.[5] CoDEX trial	Brazil	Multicenter, open-label, RCT	Aged at least 18 years Confirmed or suspected COVID-19 Receiving mechanical ventilation for ARDS	Not specified	Dexamethasone 20 mg/d for 5 d, then 10 mg/d for 5 d or until ICU discharge (*n* = 151)	Standard care (*n* = 148)	Ventilator-free days at 28 d	28 d

[a]Only two subjects were assigned 100 mg every 6 h for 7 days
[b]Based on per-protocol analysis
[c]This trial also included patients not requiring oxygen therapy

Qualität der Studien:

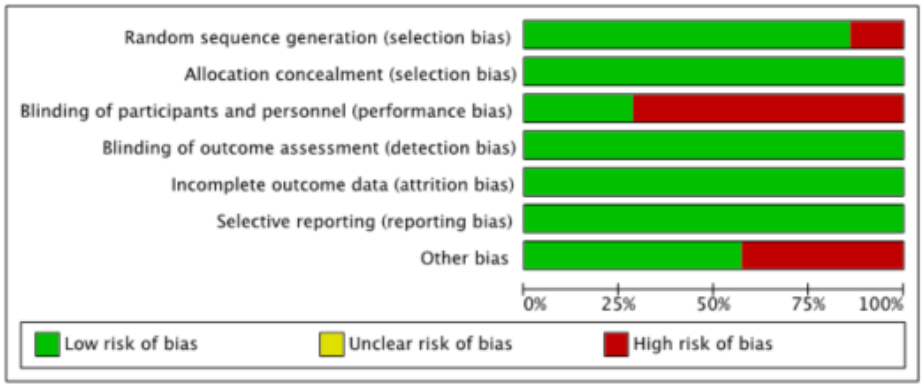


Abbildung 1: Risk of bias graph: review authors' judgement about each risk of bias item presented as percentages across all included trials

Studienergebnisse:

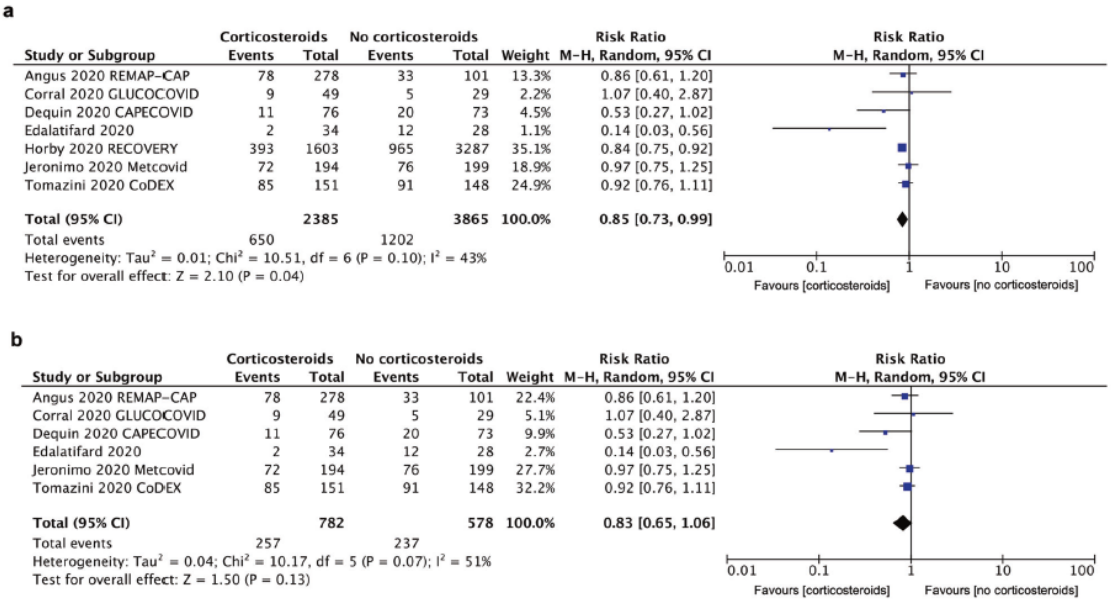


Fig. 2 Forest plot comparing corticosteroids treatment vs. no corticosteroids on all-cause mortality in severe COVID-19 patients. **a** Forest plot of all-cause mortality including all the seven trials. **b** Forest plot of all-cause mortality without RECOVERY trial. M–H Mantel–Haenszel, CI confidence interval, df degrees of freedom

Table 2. Summary of findings for outcomes comparing corticosteroids vs. no corticosteroids

No. of studies	Quality assessment					Relative effect (95% CI)	Absolute effect	Quality
	Risk of bias	Inconsistency	Indirectness	Imprecision	Publication bias			
All-cause mortality								⊕⊕⊖⊖
7	Serious[a]	None	None	None	Suspected[b]	RR 0.85 (0.73–0.99)	47 fewer per 1000 (from 3 fewer to 84 fewer)	LOW
A composite disease progression								⊕⊕⊖⊖
4	Serious[a]	None	None	None	Suspected[b]	RR 0.85 (0.77–0.93)	50 fewer per 1000 (from 23 fewer to 77 fewer)	LOW
Serious adverse events								⊕⊕⊖⊖
4	Serious[a]	None	None	None	Suspected[b]	RR 1.13 (0.54–2.38)	4 more per 1000 (from 16 fewer to 47 more)	LOW

[a]Some included studies have high risk of bias according to risk of bias results
[b]Due to small number of included trials, publication bias cannot be excluded

Anmerkung/Fazit der Autoren

In this meta-analysis of 7 RCTs and 6250 severe COVID-19 patients, pooled results suggested that corticosteroids treatment was associated with a reduction in all-cause mortality and disease progression, but not an increase in serious adverse events comparing to no corticosteroids. However, the resulted survival benefit depended on the RECOVERY trial. And suggested by TSA, additional RCTs were required to confirm the efficacy of corticosteroids to reduce all-cause mortality. Together with great heterogeneity among trials and low evidence certainty, it remains prudent to draw a definite conclusion with regard to efficacy of corticosteroids among severe COVID-19 patients.

Kommentare zum Review

- Siehe auch Pulakurthi YS et al., 2021 [17], Abeldaño Zuñiga RA et al., 2021 [1], Welte T. et al., 2021 [19], Pasin et al., 2021 [16].

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 [8].

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

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: Gültig bis Dezember 2021;

LoE/GoR

- GRADE Methodik

Sonstige methodische Hinweise

Für diese Version der Leitlinie (**Oktober 2021**) wurden zu den Themen Beatmung, Bauchlagerung, Antikoagulation, medikamentöse Therapie (monoklonale Antikörper, Kortikosteroide, Tocilizumab, Remdesivir, Rekonvaleszentplasma, Ivermectin, Azithromycin, Vitamin D, Anakinra, Januskinase (JAK)-Inhibitoren, Colchicin) und zur palliativen Behandlung systematische Recherchen durchgeführt. Empfehlungen/Statements dazu wurden abgestimmt.

Die aktuelle Version entstand im September 2021. Für folgende relevante Fragestellungen erfolgte eine Aktualisierungsrecherche: 1) Beatmung, 2) Antikoagulation, 3) Medikamentöse Therapie: Kortikosteroide, Remdesivir, Rekonvaleszentplasma, Ivermectin, SARS-CoV-2 spezifische monoklonale Antikörper, Tocilizumab, Vitamin D, Azithromycin, 4) palliative medikamentöse Therapie. Neu erstellt wurden Evidenzsynthesen zur Bauchlage (Prone position), SARS-CoV-2 spezifische monoklonale Antikörper Casirivimab und Imdevimab, Anakinra, Januskinase (JAK)-Inhibitoren und Colchicin. Zu allen diesen Themen wurden Empfehlungen bestätigt, modifiziert oder neu abgestimmt. Die restlichen Empfehlungen wurden ebenfalls bestätigt.

Diese vorliegende Leitlinie bezieht sich dementsprechend auf den gesamten stationären Versorgungsbereich. Fürden ambulanten Bereich verweisen wirauf die Empfehlungen der Deutschen Gesellschaft für Allgemeinmedizin und Familienmedizin [7]. Aus Gründen der Lesbarkeit wurde im Text die männliche Form gewählt, nichtsdestoweniger beziehen sichdie Angaben auf Angehörige jeglichen Geschlechts.

Empfehlungen

Maßnahmen bei akuter hypoxämischer respiratorischer Insuffizienz

Sauerstoffgabe, High-Flow-Sauerstofftherapie, nichtinvasive Beatmung, Bauchlagerung

EMPFEHLUNG 12 (EK, bestätigt und ergänzt 09/2021):
Ziel bei akuter hypoxämischer respiratorischer Insuffizienz bei COVID-19 ist eine adäquate Oxygenierung sicherzustellen. Es sollte eine SpO2 ≥ 92 % (bei COPD-Patienten > 88 %) erreicht werden. ⇑

EMPFEHLUNG 13 (EK, bestätigt 09/2021):
Wir schlagen vor, bei Patienten mit COVID-19 und hypoxämischer respiratorischer Insuffizienz (PaO_2/FiO_2 = 100-300 mmHg) unter kontinuierlichem Monitoring und ständiger Intubationsbereitschaft einen Therapieversuch mit High-Flow-Sauerstofftherapie (HFNC) oder CPAP/nichtinvasiver Beatmung durchzuführen. ⇑

Empfehlung 14	Evidenzbasierte Empfehlung, neu 09/2021
Empfehlungsgrad: **B ⇑**	Bei Patienten unter High-Flow-Sauerstofftherapie und CPAP/NIV sollte zusätzlich eine Bauchlagerung durchgeführt werden.
Qualität der Evidenz: Mortalität: niedrig ⊕⊕⊖⊖ Klinische Verschlechterung (kombiniert: Progress zu Intubation oder Tod): moderat ⊕⊕⊕⊖	Literatur: Ehrmann S et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. The Lancet. Respiratory medicine. 2021. doi:10.1016/s2213-2600 Rosén J et al. Awake prone positioning in patients with hypoxemic respiratory failure due to COVID-19: the PROFLO multicenter randomized clinical trial. Critical care (London, England). 2021;25(1):209. doi:10.1186/s13054-021-03602-9
	Starker Konsens

Empfehlung 15	Evidenzbasierte Empfehlung, bestätigt 09/2021
Empfehlungsgrad: **B ⇑**	Wir schlagen vor, bei Patienten mit COVID-19 und einer schwereren Hypoxämie (PaO_2/FiO_2 < 150 mmHg) und Atemfrequenzen > 30/min die Intubation und invasive Beatmung zu erwägen, bei einem PaO_2/FiO_2 von < 100 mmHg sollten im Regelfall eine Intubation und invasive Beatmung erfolgen.

Qualität der Evidenz: Mortalität: sehr niedrig ⊕⊖⊖ ⊖	Literatur: DGAI. S3-Leitlinie Invasive Beatmung und Einsatz extrakorporaler Verfahren bei akuter respiratorischer Insuffizienz. 2017. Empfehlung 1 DGP. S3-Leitlinie Nicht-invasive Beatmung als Therapie der akuten respiratorischen Insuffizienz. 2015. Empfehlung 14 und 16 COVID-19 spezifische Evidenz aus systematischer Recherche: Schünemann HJ et al. Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19: A Living Systematic Review of Multiple Streams of Evidence. Ann Intern Med. 2020;173(3):204-216. Thomas R et al. Update Alert 2: Ventilation Techniques and Risk for Transmission of Coronavirus Disease, Including COVID-19. Ann Intern Med. 2020 Dec 1;173(11):W152-W153 Grieco DL et al. Effect of Helmet Noninvasive Ventilation vs High-Flow Nasal Oxygen on Days Free of Respiratory Support in Patients With COVID-19 and Moderate to Severe Hypoxemic Respiratory Failure: The HENIVOT Randomized Clinical Trial. Jama. 2021;325(17):1731-43. doi:10.1001/jama.2021.4682 Ehrmann S et al. Awake prone positioning for COVID-19 acute hypoxaemic respiratory failure: a randomised, controlled, multinational, open-label meta-trial. The Lancet. Respiratory medicine. 2021. doi:10.1016/s2213-2600 weitere berücksichtigte Evidenz: siehe Hintergrundtext:
	Starker Konsens

Intubation

EMPFEHLUNG 16 (EK, bestätigt 09/2021):
Eine Instrumentierung der Atemwege bei COVID-19 soll ausschließlich mit vollständig angelegter persönlicher Schutzausrüstung erfolgen. ⇑⇑

STATEMENT (EK, bestätigt 09/2021):
Für den in der indirekten Laryngoskopie Erfahrenen ist der Einsatz der Videolaryngoskopie bei COVID-19 eine Möglichkeit, mit einer größeren Distanz zu den Atemwegen der Patienten arbeiten zu können.

Invasive Beatmung und adjuvante Maßnahmen

EMPFEHLUNG 17 (EK, bestätigt 09/2021):
Bei beatmeten Patienten mit COVID-19 und ARDS sollte das Tidalvolumen ≤ 6 ml/kg Standardkörpergewicht betragen, der endinspiratorische Atemwegsdruck ≤ 30 cm H_2O. ⇑

EMPFEHLUNG 18 (EK, bestätigt 09/2021):
Für die orientierende Einstellung des PEEP bei COVID-19 sollte die FiO_2/PEEP-Tabelle des ARDS-Networks berücksichtigt werden. Durch ein engmaschiges Monitoring kann der PEEP der individuellen Situation des Patienten angepasst werden. ⇑

Thromboembolieprophylaxe /Antikoagulation

Thromboembolieprophylaxe

EMPFEHLUNG 19A (EK, bestätigt 09/2021):
Hospitalisierte Patienten mit COVID-19 sollen in Abwesenheit von Kontraindikationen eine standardmäßige medikamentöse Thromboembolieprophylaxe mit niedermolekularem Heparin erhalten. Alternativ kann Fondaparinux zur Anwendung kommen. ⇑⇑

Empfehlung 19B	Evidenzbasierte Empfehlung, neu 09/2021
Empfehlungsgrad: B⇓	Bei hospitalisierten Patienten mit COVID-19 sollte keine halbtherapeutische Antikoagulation erfolgen.
Qualität der Evidenz: Jegliches thrombotisches Ereignis oder Tod innerhalb von 30 Tagen: niedrig ⊕⊖ ⊖⊖ Erhöhtes Risiko für schwere Blutung: niedrig ⊕⊖ ⊖⊖	Literatur: Sadeghipour et al. Intermediate-Dose versus Standard-Dose Prophylactic Anticoagulation in Patients with COVID-19 Admitted to the Intensive Care Unit: 90-Day Results from the INSPIRATION Randomized Trial. Thromb Haemost. 2021 Apr 17. doi: 10.1055/a-1485-2372. Perepu et al. Standard prophylactic versus intermediate dose enoxaparin in adults with severe COVID-19: A multi-center, open-label, randomized controlled trial. J Thromb Haemost. 2021 Sep;19(9):2225-2234. doi: 10.1111/jth.15450.
	Starker Konsens

Nichtintensivpflichtige Patienten

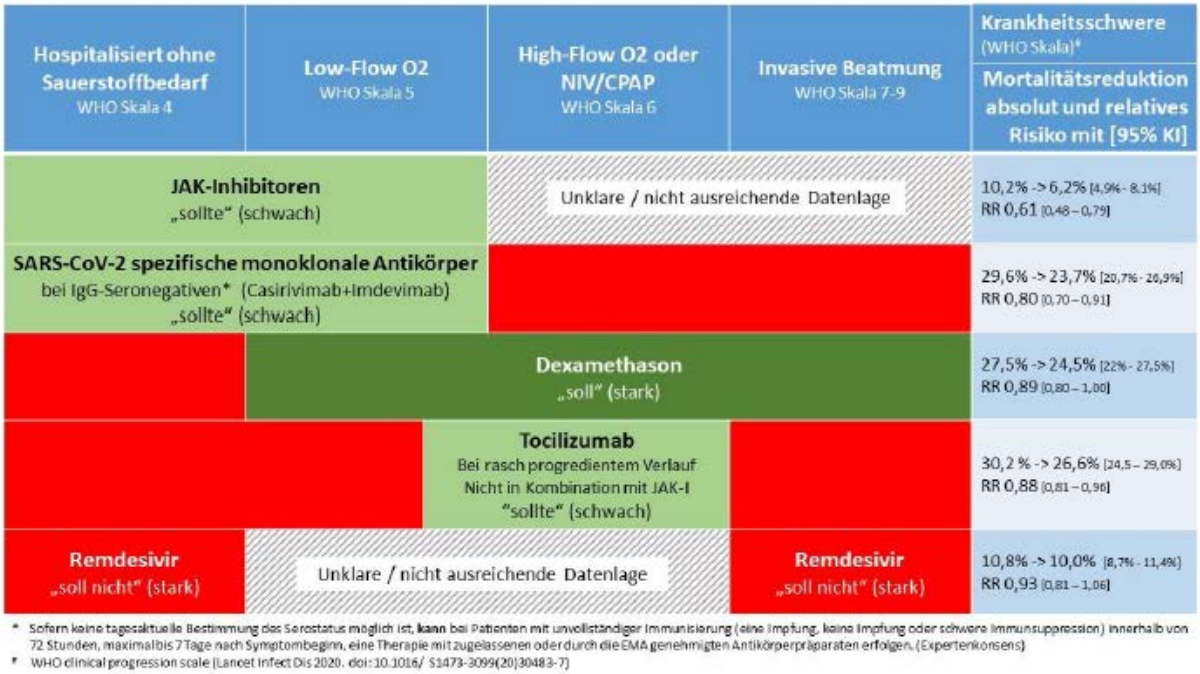
EMPFEHLUNG 19C (EK, geändert 09/2021):
Bei hospitalisierten, nichtintensivpflichtigen Patienten mit COVID-19 und erhöhtem Risiko (z.B. D-Dimere ≥ 2 mg/l) kann bei niedrigem Blutungsrisiko eine therapeutische Antikoagulation, präferenziell mit NMH oder UFH, erwogen werden. ⇔

Intensivpflichtige Patienten

Empfehlung 20	Evidenzbasierte Empfehlung, neu 09/2021
Empfehlungsgrad: B ⇓	Bei Intensivpatienten ohne spezifische Indikation (z.B. Lungenembolien) sollte eine therapeutische Antikoagulation nicht erfolgen.
Qualität der Evidenz: Thrombot. Ereignisse oder Blutung: niedrig ⊕⊖⊖⊖ Schwere Blutung: niedrig ⊕⊕⊖⊖	Literatur: Goligher EC et al. Therapeutic Anticoagulation with Heparin in Critically Ill Patients with Covid-19. N Engl J Med. 2021 Aug 26;385(9):777-789. doi: 10.1056/NEJMoa2103417. Lemos ACB, do Espírito Santo DA, Salvetti MC, et al. Therapeutic versus prophylactic anticoagulation for severe COVID-19: A randomized phase II clinical trial (HESACOVID). Thrombosis research. 2020;196:359-66. doi:10.1016/j.thromres.2020.09.026 Lopes RD, et al.; ACTION Coalition COVID-19 Brazil IV Investigators. Therapeutic versus prophylactic anticoagulation for patients admitted to hospital with COVID-19 and elevated D-dimer concentration (ACTION): an open-label, multicentre, randomised, controlled trial. Lancet. 2021 Jun 12;397(10291):2253-2263. doi: 10.1016/S0140-6736(21)01203-4.
	Starker Konsens

Medikamentöse Therapie

Spezifische medikamentöse Therapie



* Sofern keine tagesaktuelle Bestimmung des Serostatus möglich ist, kann bei Patienten mit unvollständiger Immunisierung (eine Impfung, keine Impfung oder schwere Immunsuppression) innerhalb von 72 Stunden, maximal bis 7 Tage nach Symptombeginn, eine Therapie mit zugelassenen oder durch die EMA genehmigten Antikörperpräparaten erfolgen. (Expertenkonsens)

* WHO clinical progression scale (Lancet Infect Dis 2020. doi: 10.1016/ S1473-3099(20)30483-7)

Abbildung 2: Übersicht der Empfehlungen der medikamentösen Therapie bei COVID-19, abhängig von der Krankheitsschwere.

Hinweis: Es wird darauf verwiesen, dass die Mehrheit der Arzneimittel (derzeit nur Remdesivir) trotz Empfehlung in der Leitlinie nicht zur Anwendung der Covid-19 Therapie zugelassen ist.

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% (21,8% - 24,9%) RR 0,98 (0,92 – 1,05)	High
Ivermectin	Soll nicht	9,6% –> 5,8% (1,3% - 24,1%) RR 0,6 (0,14 – 2,51)	Very low
Vitamin D	Soll nicht	Not pooled (heterogeneity)	Very low
Azithromycin	Soll nicht	22,3% –> 21,9% (20,1% - 23,6%) RR 0,98 (0,9 – 1,06)	High
Bamlanivimab Monotherapie	Soll nicht	2,7% –> 3,8% (1,1% - 13,0%) RR 1,39 (0,4 – 4,83)	Low
Anakinra	Soll nicht	23,6% –> 21,9% (11,1% - 43,2%) RR 0,93 (0,47 – 1,83)	Moderate
Colchicin	Soll nicht	20,7% –> 20,7% (19,3% - 22,4%) RR 1 (0,93 – 1,08)	Moderate

Tabelle 1: Evidenzbasierte Negativempfehlungen zur medikamentösen Therapie bei COVID-19.

Antivirale Therapieansätze

Monoklonale Antikörper: Casirivimab/Imdevimab

Empfehlung 21	**Evidenzbasierte Empfehlung, neu 09/2021**
Empfehlungsgrad: **B⇑**	**Bei hospitalisierten IgG-seronegativen Patienten mit Covid-19-Erkrankung und fehlendem Sauerstoffbedarf oder maximal Low-Flow-Sauerstoff sollte eine Therapie mit der Kombination aus den SARS-CoV-2 spezifischen monoklonalen Antikörpern Casirivimab und Imdevimab erfolgen.**
Qualität der Evidenz: Letalität: moderat ⊕⊕⊕⊖ Progression (Beatmung oder Tod): moderat ⊕⊕⊕⊖	Literatur: Kreuzberger et al. SARS-CoV-2-neutralising monoclonal antibodies for treatment of COVID-19. Cochrane Database Syst Rev. 2021 Sep 2;9(9):CD013825. doi: 10.1002/14651858.CD013825.pub2.
	Starker Konsens

Sondervotum der DGKJ:

Zu dieser Empfehlung legte die DGKJ folgendes Sondervotum ein: Die DGKJ spricht sich gegen diese Empfehlung aus.

Monoklonale Antikörper bei unbekanntem IgG-Serostatus

EMPFEHLUNG 22 (EK, neu 09/2021):
Sofern keine tagesaktuelle Bestimmung des Serostatus möglich ist, kann bei hospitalisierten Patienten mit unvollständiger Immunisierung* und früher SARS-CoV-2 Infektion, innerhalb von 72 Stunden, maximal jedoch bis 7 Tage nach Symptombeginn, eine Therapie mit SARS-CoV-2 spezifischen monoklonalen Antikörpern erfolgen. ⟺
* Keine oder unvollständige aktive Immunisierung mit einem zugelassenen SARS-CoV-2 Vakzin oder Vorliegen einer schweren Immunsuppression.

Sondervotum der DGKJ:

Zu dieser Empfehlung legte die DGKJ folgendes Sondervotum ein: Die DGKJ spricht sich gegen diese Empfehlung aus.

Monoklonale Antikörper: Bamlanivimab-Monotherapie

Empfehlung 23	**Evidenzbasierte Empfehlung, aktualisiert 09/2021**
Empfehlungsgrad: **B ⇓**	**Der SARS-CoV-2 spezifische monoklonale Antikörper Bamlanivimab soll nicht bei erwachsenen Patienten mit einer in der PCR nachgewiesenen moderaten bis schweren SARS-CoV-2-Infektion zur Monotherapie im stationären Bereich eingesetzt werden.**
Qualität der Evidenz: Letalität: niedrig ⊕⊕⊖⊖ Unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖	Literatur: Lundgren JD et al. A Neutralizing Monoclonal Antibody for Hospitalized Patients with Covid-19. The New England journal of medicine. 2020. doi:10.1056/NEJMoa2033130
	Starker Konsens

Remdesivir

Empfehlung 24	**Evidenzbasierte Empfehlung, aktualisiert 09/2021**
Empfehlungsgrad: **A ⇓⇓**	**Remdesivir soll bei Patienten mit COVID-19 ohne Sauerstoffbedarf und bei invasiv beatmeten Patienten nicht eingesetzt werden.**

	Ergänzendes Statement bestätigt 09/2021 **Bei hospitalisierten Patienten mit COVID-19 Pneumonie und erforderlicher Low-Flow/High-Flow-Sauerstofftherapie oder nichtinvasiver Beatmung, kann weder eine Empfehlung dafür noch gegen eine Therapie mit Remdesivir abgegeben werden.**
Qualität der Evidenz: 28d Sterblichkeit: moderat ⊕⊕⊕⊖ SAE – Rate: moderat ⊕⊕⊕⊖ Daten zur klinischen Verschlechterung/Verbesserung: niedrig ⊕⊕⊖⊖	Literatur: Beigel JH et al. Remdesivir for the Treatment of Covid-19 - Final Report. The New England journal of medicine. 2020. doi:10.1056/NEJMoa2007764 Pan H et al. Repurposed Antiviral Drugs for Covid-19 - Interim WHO Solidarity Trial Results. The New England journal of medicine. 2020. doi:10.1056/NEJMoa2023184 Spinner CD et al. Effect of Remdesivir vs Standard Care on Clinical Status at 11 Days in Patients with Moderate COVID-19: A Randomized Clinical Trial. Jama. 2020;324(11):1048-57. doi:10.1001/jama.2020.16349 Wang Y et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet (London, England). 2020;395(10236):1569-78. doi:10.1016/s0140-6736(20)31022-9 Ansems K. et al. Remdesivir for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD014962. doi: 10.1002/14651858.CD014962.
	Starker Konsens

Rekonvaleszentenplasma

Empfehlung 25	**Evidenzbasierte Empfehlung, bestätigt 09/2021**
Empfehlungsgrad: **A ⇓⇓**	**Rekonvaleszentenplasma soll nicht bei hospitalisierten Patienten mit COVID-19 eingesetzt werden. Zu spezifischen Subgruppen lässt sich auf Basis der derzeitigen Evidenz keine Empfehlung ableiten.**
Qualität der Evidenz: 28 Tage Letalität: ⊕⊕⊕⊕ Unerwünschte Ereignisse: ⊕⊕⊖⊖	Literatur: Piechotta et al. Convalescent plasma or hyperimmune immunoglobulin for people with COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021 May 20;5(5):CD013600. doi: 10.1002/14651858.CD013600.pub4.
	Starker Konsens

Azithromycin

Empfehlung 26	Evidenzbasierte Empfehlung, bestätigt 09/2021
Empfehlungsgrad: **A ⇓⇓**	**Azithromycin soll nicht bei hospitalisierten Patienten zur antiviralen COVID-19 Therapie verabreicht werden.**
Qualität der Evidenz: Letalität: hoch ⊕⊕ ⊕⊕	Literatur:
Unerwünschte Ereignisse: moderat ⊕⊕⊕⊖	RECOVERY Collaborative Group. Azithromycin in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet (London, England). 2021. doi:10.1016/s0140-6736(21)00149-5 Furtado RHM et al. Azithromycin in addition to standard of care versus standard of care alone in the treatment of patients admitted to the hospital with severe COVID-19 in Brazil (COALITION II): a randomised clinical trial. Lancet (London, England). 2020;396(10256):959-67. doi:10.1016/s0140-6736(20)31862-6 Cavalcanti AB et al. Hydroxychloroquine with or without Azithromycin in Mild-to-Moderate Covid-19. The New England journal of medicine. 2020;383(21):2041-52. doi:10.1056/NEJMoa2019014 Sekhavati E et al. Safety and effectiveness of azithromycin in patients with COVID-19: An open-label randomised trial. International journal of antimicrobial agents. 2020;56(4):106143. doi:10.1016/j.ijantimicag.2020.106143 Popp M et al. Antibiotics for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 10. Art. No.: CD015025. DOI: 10.1002/14651858.CD015025 (in press)
	Starker Konsens

Ivermectin

Empfehlung 27	Evidenzbasierte Empfehlung, bestätigt 09/2021
Empfehlungsgrad: **A⇓⇓**	**Ivermectin soll bei hospitalisierten Patienten nicht zur COVID-19-Behandlung verabreicht werden.**
Qualität der Evidenz: Zeit bis zur Viruselimination: sehr niedrig ⊕⊖ ⊖⊖ Dauer des Krankenhausaufenthalts: sehr niedrig ⊕⊖ ⊖⊖	Literatur: Ahmed S et al. A five-day course of ivermectin for the treatment of COVID-19 may reduce the duration of illness. International journal of infectious diseases : IJID : official publication of the International Society for Infectious Diseases. 2021;103:214-6. doi:10.1016/j.ijid.2020.11.191 Popp M et al. Ivermectin for preventing and treating COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 7. Art. No.: CD015017. DOI: 10.1002/14651858.CD015017.pub2.
	Starker Konsens

Immunmodulatorische Therapieansätze

Kortikosteroide

Empfehlung 28A+B	Evidenzbasierte Empfehlung, aktualisiert 09/2021
Empfehlungsgrad: **A ⇑⇑**	**Bei Patienten mit COVID-19- und Sauerstoff-Bedarf (Low-Flow, High-Flow, Nichtinvasive Beatmung/CPAP, invasive 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 moderater Erkrankung (hospitalisiert ohne Notwendigkeit einer Sauerstoffgabe soll keine Therapie mit systemischen Kortikosteroiden erfolgen.**
Qualität der Evidenz: 28 Tage Letalität: moderat ⊕⊕⊕⊖ Unerwünschte Ereignisse: Sehr niedrig ⊕⊖⊖⊖	Literatur: Horby P. et al. Dexamethasone in Hospitalized Patients with Covid-19 - Preliminary Report. The New England journal of medicine. 2020. doi:10.1056/NEJMoa2021436 Tomazini BM et al. Effect of Dexamethasone on Days Alive and Ventilator-Free in Patients With Moderate or Severe Acute Respiratory Distress Syndrome and COVID-19: The CoDEX Randomized Clinical Trial. Jama. 2020. doi:10.1001/jama.2020.17021 Edalatifard M et al. Intravenous methylprednisolone pulse as a treatment for hospitalised severe COVID-19 patients: results from a randomised controlled clinical trial. The European respiratory journal. 2020;56(6). doi:10.1183/13993003.02808-2020
	Angus DC et al. Effect of Hydrocortisone on Mortality and Organ Support in Patients With Severe COVID-19: The REMAP-CAP COVID-19 Corticosteroid Domain Randomized Clinical Trial. Jama. 2020;324(13):1317-29. doi:10.1001/jama.2020.17022 Wagner C et al. Systemic corticosteroids for the treatment of COVID-19. Cochrane Database of Systematic Reviews 2021, Issue 8. Art. No.: CD014963. doi: 10.1002/14651858.CD014963.
	Starker Konsens

Januskinase (JAK) – Inhibitoren

Empfehlung 29 A+B	**Evidenzbasierte Empfehlung, Neu 09/2021**
Empfehlungsgrad: **B ⇑**	**Januskinase (JAK) - Inhibitoren sollten bei Patienten mit COVID-19-Erkrankung ohne Sauerstoffbedarf oder mit Low-Flow-Sauerstoffbedarf unter Beachtung der Kontraindikationen eingesetzt werden.**
⇓⇓	**JAK-Inhibitoren sollen nicht als Kombinationstherapie mit Tocilizumab eingesetzt werden.**
Qualität der Evidenz: Letalität: hoch ⊕⊕⊕⊕ Klinische Verschlechterung: moderat ⊕⊕⊕⊖ Unerwünschte Ereignisse: moderat ⊕⊕⊕⊖ Spezielle AEs (Myelosuppression, GI-Perforationen etc.) sehr niedrig ⊕⊖⊖⊖	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. Patrícia O et al. N Engl J Med. 2021 Jul 29;385(5):406-415. doi: 10.1056/NEJMoa2101643. Epub 2021 Jun 16. 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

Tocilizumab (TCZ)

Empfehlung 30 A+B+C	**Evidenzbasierte Empfehlung, aktualisiert 09/2021**
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.**
⇓	**Tocilizumab soll nicht als Kombinationstherapie mit JAK-Inhibitoren angewendet werden.**
Qualität der Evidenz: 28d Letalität: moderat ⊕⊕⊕⊖ Vermeidung der Zunahme der Krankheitsschwere (Progress zu	Literatur: Tocilizumab in patients admitted to hospital with COVID-19 (RECOVERY): a randomised, controlled, open-label, platform trial. Lancet. 2021;397(10285):1637-45. doi:10.1016/s0140-6736(21)00676-0

notwendiger Invasiver Beatmung): moderat ⊕⊕⊕⊖ Schwere unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖ Unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖	Gordon AC et al. . Et al. Interleukin-6 Receptor Antagonists in Critically Ill Patients with Covid-19. N Engl J Med. 2021;384(16):1491-502. doi:10.1056/NEJMoa2100433 Rosas IO et al. Tocilizumab in Hospitalized Patients with Severe Covid-19 Pneumonia. N Engl J Med. 2021 Apr 22;384(16):1503-1516. doi: 10.1056/NEJMoa2028700. Epub 2021 Feb 25. Ghosn L et al. Interleukin-6 blocking agents for treating COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021 Mar 18;3:CD013881. doi: 10.1002/14651858.CD013881. PMID: 33734435.
	Starker Konsens

Anakinra

Empfehlung 31	**Evidenzbasierte Empfehlung, neu 09/2021**
Empfehlungsgrad: **A⇓⇓**	**Anakinra soll nicht bei hospitalisierten Patienten zur COVID-19-Behandlung verabreicht werden**
Qualität der Evidenz: Letalität: moderat ⊕⊕⊕⊖ Progression (Invasive Beatmung oder Tod):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.
	Starker Konsens

Sonstige Therapieansätze

Vitamin D3

Empfehlung 32	**Evidenzbasierte Empfehlung, bestätigt 09/2021**
Empfehlungsgrad: **A ⇓⇓**	**Vitamin D_3 soll nicht bei hospitalisierten Patienten zur COVID-19-Behandlung verabreicht werden.**
Qualität der Evidenz: Klinische Verschlechterung: niedrig ⊕⊕⊖⊖ Unerwünschte Ereignisse: sehr niedrig ⊕⊖⊖⊖	Literatur: Entrenas Castillo M et al. Effect of calcifediol treatment and best available therapy versus best available therapy on intensive care unit admission and mortality among patients hospitalized for COVID-19: A pilot randomized clinical study. The Journal of steroid biochemistry and molecular biology. 2020;203:105751. doi:10.1016/j.jsbmb.2020.105751 Murai IH et al. Effect of a Single High Dose of Vitamin D3 on Hospital Length of Stay in Patients With Moderate to Severe COVID-19: A Randomized Clinical Trial. Jama. 2021. doi:10.1001/jama.2020.26848 Stroehlein et al. Vitamin D supplementation for the treatment of COVID-19: a living systematic review. Cochrane Database Syst Rev. 2021 May 24;5(5):CD015043. doi: 10.1002/14651858.CD015043.
	Starker Konsens

Colchicin

Empfehlung 33	Evidenzbasierte Empfehlung, neu 09/2021
Empfehlungsgrad: **A ⇓⇓**	**Colchicin soll nicht bei hospitalisierten Patienten zur COVID-19-Therapie eingesetzt werden.**
Qualität der Evidenz: Letalität: moderat⊕⊕⊕⊖ Verbesserung des klinischen Status: moderat⊕⊕⊕⊖	Literatur: Deftereos SG et al. JAMA Netw Open. 2020 Jun 1;3(6):e2013136. doi: 10.1001/jamanetworkopen.2020.13136. Lopes MI et al. RMD Open. 2021 Feb;7(1):e001455. doi: 10.1136/rmdopen-2020-001455.
	Starker Konsens

Persistierende Symptome

EMPFEHLUNG 34 (EK, bestätigt 09/2021):
Bei Patienten mit stationär behandelter COVID-19 Erkrankung sollte nach 8-12 Wochen eine Nachuntersuchung bezüglich Langzeitfolgen erfolgen. ⇑

Ethische und palliativmedizinische Aspekte

Empfehlung 35	Evidenzbasierte Empfehlung, bestätigt 09/2021
Empfehlungsgrad: **A ⇑⇑**	**Patienten mit COVID-19 sollen zur palliativen medikamentösen Symptombehandlung bei** • **Luftnot: Opioide** • **Angst: Benzodiazepine** • **Rasselatmung: Anticholinergika** • **Delir: Neuroleptika** **erhalten.**
Qualität der Evidenz: Symptomlinderung: sehr niedrig ⊕⊖⊖ ⊖	Literatur: Alderman B et al. An audit of end-of-life symptom control in patients with corona virus disease 2019 (COVID-19) dying in a hospital in the United Kingdom. Palliat Med. 2020;34(9):1249-55. doi:10.1177/0269216320947312 (278) Lovell N et al. Characteristics, Symptom Management, and Outcomes of 101 Patients With COVID-19 Referred for Hospital Palliative Care. J Pain Symptom Manage. 2020;60(1):e77-e81. doi:10.1016/j.jpainsymman.2020.04.015 (279) Hetherington L et al. COVID-19 and Hospital Palliative Care - A service evaluation exploring the symptoms and outcomes of 186 patients and the

	impact of the pandemic on specialist Hospital Palliative Care. Palliat Med. 2020;34(9):1256-62. doi:10.1177/0269216320949786 (280) Strang P et al. Symptom Relief Is Possible in Elderly Dying COVID-19 Patients: A National Register Study. J Palliat Med. 2021;24(4):514-9. doi:10.1089/jpm.2020.0249 (281) Strang P et al. COVID-19: Symptoms in Dying Residents of Nursing Homes and in Those Admitted to Hospitals. J Palliat Med. 2021. doi:10.1089/jpm.2020.0688 (282)
	Starker Konsens

Zusätzliche Informationen aus DEGAM, 2021 [7].

Neues Coronavirus: Informationen für die hausärztliche Praxis; S1-Leitlinie, Version 18

Klinische Hinweise zur Behandlung von COVID-19-Fällen

7.3 Arzneimitteltherapie

Für junge, ansonsten gesunde Menschen, die sich mit Corona infiziert haben, reichen in der Regel supportive Maßnahmen aus.
Für alte und/oder vorerkrankte Patientinnen und Patienten (z. B. Adipositas, Diabetes, Hypertonie, COPD, Herz- und Nierenkrankheiten, Immunsuppression) bieten sich folgende Therapie**optionen** an – mit dem Ziel, einen schweren Krankheitsverlauf zu verhindern. Es handelt sich meist um **off-label-Verordnungen**, da die aufgeführten Arzneimittel für die Indikation Covid-19 nicht zugelassen sind:

7.3.1 Empfehlung

Wenn bei alten und/oder vorerkrankten Patientinnen und Patienten mit SARS-CoV-2 Infektion die D-Dimere um mind. 1.5-2 x Normwert erhöht sind, sollte eine prophylaktische Heparinisierung erfolgen.
Dosierung 1 x 4.000 IE/d Enoxaparin s.c. (falls BMI > 35 bzw. KG > 100 kg oder früher stattgehabte Thromboembolie: 2 x 4.000 IE/d).
Achtung: Nicht bei oraler Antikoagulation; bei ASS-Dauertherapie: PPI-Prophylaxe ab 65 J.

Quellen: https://pubmed.ncbi.nlm.nih.gov/33249247/
https://www.bmj.com/content/372/bmj.n311/related
https://gth-online.org/wp-content/uploads/2021/04/GTH-Stellungnahme-AstraZeneca_4-1-2021.pdf

7.3.2 Empfehlung

Bei alten und/oder vorerkrankten Patientinnen und Patienten kann bei SARS-CoV-2-Infektion zwecks Prophylaxe eines schweren Verlaufs Budesonid-Inhalation: 2 x 800 µg/d für 7-14 Tage erfolgen.

Quellen: https://www.thelancet.com/journals/lanres/article/PIIS2213-2600(21)00160-0/fulltext; https://pubmed.ncbi.nlm.nih.gov/33068560/

7.3.3 Empfehlung

Bei alten und/oder vorerkrankten Patientinnen und Patienten kann bei SARS-CoV-2-Infektion zwecks Prophylaxe eines schweren Verlaufs Fluvoxamin erwogen werden: Beginn mit 1 x 50 mg möglichst abends, für die nächsten 14 Tage 2 x 50-100 mg/d (je nach Verträglichkeit).

Quellen: https://jamanetwork.com/journals/jama/fullarticle/2773108; https://academic.oup.com/ofid/article/8/2/ofab050/6124100

- **Monoklonale Antikörper** (Bamlanivimab, Etesevimab und Kombination aus Casirivimab und Imdevimab) sind in Deutschland nicht zugelassen, aber von der Bundesregierung gekauft worden und in Krankenhäusern bzw. speziellen Ambulanzen verfügbar. Die Wirksamkeit der Präparate erscheint nach allen verfügbaren Daten zweifelhaft. Kinder ab 12 Jahren (und 40 kg KG) und Erwachsene mit milder bis moderater COVID-19-Erkrankung können von den Hausärztinnen und Hausärzten zur Therapie überwiesen werden, sofern sie Risikofaktoren für einen schweren COVID-19-Verlauf aufweisen (z. B. Alter über 60 Jahre, Immunsuppression, Adipositas, kardiovaskuläre Erkrankungen). Ihr Einsatz erfolgt als individueller Heilversuch einmalig in der Frühphase der Erkrankung (<10 Tage nach Symptombeginn und ≤ 3 Tage nach einem positiven PCR-Test). Die Therapie selbst erfolgt stationär oder in spezifischen Ambulanzen (je nach Bundesland und Region unterschiedlich geregelt) – und sollte nur im Rahmen klinischer Studien erfolgen.
  https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Therapieuebersicht.pdf?__blob=publicationFile

  Gegen die aktuell in Deutschland dominierende britische Virusvariante B.1.1.7 sind ide-monoklonalen Antikörper in-vitro wirksam.
  https://www.rki.de/DE/Content/InfAZ/N/Neuartiges_Coronavirus/COVRIIN_Dok/Monoklonale_AK.pdf?__blob=publicationFile

- Vitamin D: Aufgrund der vorliegenden wissenschaftlichen Belege, die für eine verbesserte Abwehr respiratorischer Infekte sprechen – wahrscheinlich auch für Covid-19 zutreffend – erscheint es ratsam, dass alle älteren Personen (insbesondere Altenheimbewohner) prophylaktisch 1.000 (-2.000) IE/Tag einnehmen (kostet als Selbstmedikation pro Tag nur wenige Cent). Bis auf seltene Ausnahmen ist eine Bestimmung des Vitamin-D-Spie-

gels dabei allerdings nicht sinnvoll - die Substitution verursacht (bis max. 4.000 IE/Tag) keine unerwünschten Wirkungen. Von der Einnahme oder parenteralen Gabe von hochdosierten Präparaten raten wir ab.
https://pubmed.ncbi.nlm.nih.gov/33401034/
https://pubmed.ncbi.nlm.nih.gov/33515005/

- Für eine therapeutische Gabe von Vitamin D3 bei nachgewiesener Covid-19-Erkrankung liegt bislang keine belastbare Evidenz vor. Weltweit laufen zahlreiche randomisiert-kontrollierte Studien, die in absehbarer Zeit entsprechende Daten liefern werden.

Weitere mögliche Maßnahmen (nicht Bestandteil dieser Leitlinie) sind in einem Text aufgeführt, der beim Bayerischen Hausärzteverband abrufbar ist – dort findet sich auch eine für alle aufgeführten Optionen begründende, ausführliche Literaturliste:
https://www.hausaerzte-bayern.de/images/aktuell/covid19/Ambulante_Therapieoptionen_bei_Covid-19_Vs_3_12-4-2021.pdf

- Fieber sollte bei Atemwegserkrankungen grundsätzlich nicht reflexhaft gesenkt werden. Wenn eine Fiebersenkung notwendig ist, sollte Paracetamol anstelle von NSAR verabreicht werden. Die Vorbehalte gegenüber NSAR gelten grundsätzlich für ältere Patientinnen und Patienten wegen des Spektrums unerwünschter Wirkungen (kardial, gastrointestinal) – unabhängig von COVID-19.

Infectious Diseases Society of America (IDSA), 2021 [9]

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 5.5.0

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 from 2019 through September 18, 2020.
- Letzte Aktualisierung: 01.11.2021

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.

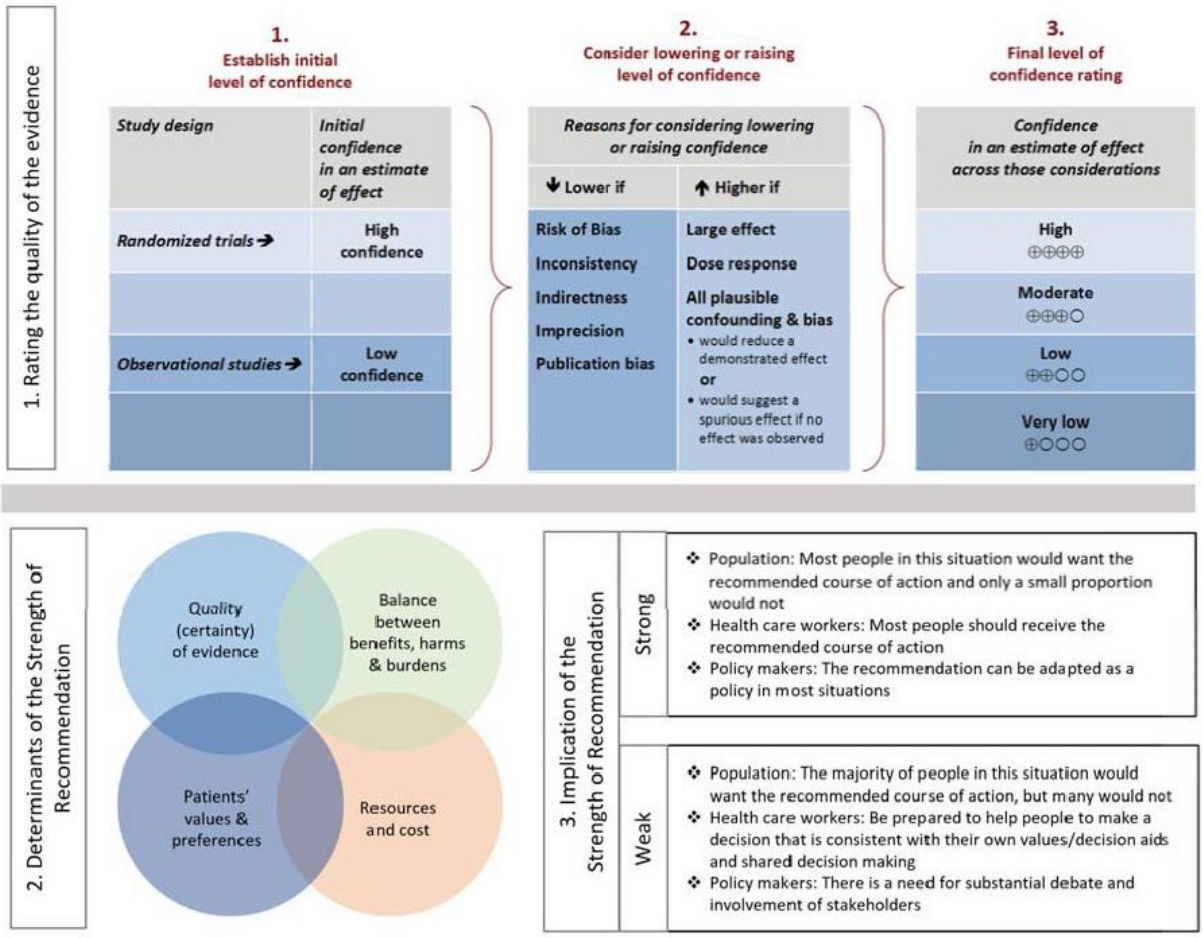


Abbildung 1: Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)

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.

Recommendations

Hydroxychloroquine/Chloroquine; Hydroxychloroquine/Chloroquine plus Azithromycin

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.

Hydroxychloroquine as Post-Exposure Prophylaxis

Recommendation 3: In persons exposed to COVID-19, the IDSA guideline panel recommends against hydroxychloroquine. (Strong recommendation, Moderate certainty of evidence)

Lopinavir/Ritonavir

Recommendation 4: 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

Recommendation 5: 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 6: 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 7: 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)**

Severity definitions

*Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS

**Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

***Non-severe illness is defined as patient with a SpO_2 > 94% not requiring supplemental oxygen.

<u>Interleukin-6 Inhibitors</u>

Recommendation 8: 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)**

Remarks:

- 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 9: 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.

Severity definitions

*Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.

**Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

Convalescent Plasma

Recommendation 10: Among patients hospitalized with COVID-19, the IDSA guideline panel suggests against COVID-19 convalescent plasma. (Conditional recommendation, Low certainty of evidence)

Recommendation 11: Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)

Remdesivir

Recommendation 12a: 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 SpO_2 ≤94% on room air.

Recommendation 12b: 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)

Recommendation 13: 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 14: In patients with COVID-19 admitted to the hospital without the need for supplemental oxygen and oxygen saturation >94% on room air, the IDSA panel suggests against the routine use of remdesivir. (Conditional recommendation, Very low certainty of evidence)

Famotidine

Recommendation 15: 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)

Neutralizing Antibodies for Prophylaxis

Recommendation 16: In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests post-exposure casirivimab/imdevimab rather than no casirivimab/imdevimab. (Conditional recommendation, low certainty of evidence)

Remarks:

- Dosing for casirivimab/imdevimab is casirivimab 600 mg & imdevimab 600 mg IV or SC once.
- In the trial considered for this recommendation, participants were enrolled within 96 hours after a household contact received a diagnosis of SARS-CoV-2 infection.

Neutralizing Antibodies for Treatment

Recommendation 17: 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)

Remarks:

- 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.

Recommendation 18: Among hospitalized patients with severe COVID-19, the IDSA guideline panel recommends against bamlanivimab monotherapy. (Strong recommendation, Moderate certainty of evidence)

Janus Kinase Inhibitors

Recommendation 19: 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)

Remarks:

- 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 20: 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 SpO_2 ≤94% on room air, including patients on supplemental oxygen, oxygen through a high-flow device, or non-invasive ventilation.

Tofacitinib

Recommendation 21: 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)

Remarks:

- 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 SpO_2 ≤94% on room air, including patients on supplemental oxygen or oxygen through a high-flow device.

Ivermectin

Recommendation 22: 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 23: 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

Recommendation 24: Among ambulatory patients with COVID-19, the IDSA guideline panel recommends fluvoxamine only in the context of a clinical trial. (Knowledge gap)

National COVID-19 Clinical Evidence Taskforce, 2021 [13].

Australian guidelines for the clinical care of people with COVID-19: version 45.1

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: 03.11.2021

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

6.1 Recommended disease-modifying treatments

6.1.1 Budesonide

6.1.1.1 Budesonide for adults

Conditional recommendation

Updated

Consider using inhaled budesonide for the treatment of symptomatic COVID-19 in adults who do not require oxygen and who have one or more risk factors for disease progression.

In patients with confirmed COVID-19 who do not require oxygen but who are subsequently hospitalised due to disease progression, budesonide probably decreases the requirement of supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial [569], in which adults were treated with inhaled budesonide (by breath actuated inhaler) 800 µg twice daily for up to 14 days. Based on the inclusion criteria for this trial, risk factors for disease progression include age ≥ 65 years or ≥ 50 years with one or more of the following comorbidities:

- *Diabetes (not treated with insulin)*
- *Heart disease and/or hypertension*
- *Asthma or lung disease*
- *Weakened immune system due to a serious illness or medication (e.g. chemotherapy)*
- *Mild hepatic impairment*
- *Stroke or other neurological problem*

Approximately 11% and 1% of participants had received one or two doses of vaccine at enrolment, respectively, however results were not reported separately for this population.

Budesonide is safe to use in pregnant and breastfeeding women.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.2 Casirivimab plus imdevimab (Ronapreve/REGEN-COV)

6.1.2.1 Casirivimab plus imdevimab (Ronapreve/REGEN-COV) for adults

Conditional recommendation

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

In patients hospitalised with moderate to critical COVID-19 who are seronegative (no detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

The Taskforce notes that the RECOVERY trial administered a single intravenous 8000 mg dose of REGEN-COV (4000 mg casirivimab plus 4000 mg imdevimab in 250 ml 0.9% saline) and assessed baseline serostatus using the Oxford immunoassay, the use of which has been supported by the UK National SARS-CoV-2-Serology Assay Evaluation Group [519].

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Not recommended

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

In patients hospitalised with moderate to critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab probably has little impact on mortality, the need for invasive mechanical ventilation and discharge from hospital. Because of this, the Taskforce recommends against the use of casirivimab plus imdevimab in hospitalised patients who are seropositive.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation

New

Consider using casirivimab plus imdevimab for the treatment of COVID-19 in **mild outpatients** who have one or more risk factors for disease progression within 7 days of onset of symptoms.

In adult outpatients with mild COVID-19, casirivimab plus imdevimab probably reduces hospitalisation and incidence of adverse events. Because of this, the Taskforce gives a conditional recommendation for casirivimab plus imdevimab both within and outside the context of a randomised trial.

Included data comes from the three-phase REGEN-COV trial [511][579] in which patients with one or more risk factors for disease progression received either 1200 mg, 2400 mg or 8000 mg casirivimab plus imdevimab. Based on inclusion criteria of the trial, risk factors for disease progression include:

- *Age ≥ 50 years*
- *Obesity (≥ 30 kg/m2)*
- *Cardiovascular disease (including hypertension)*
- *Chronic lung disease (including asthma)*
- *Type 1 or 2 diabetes mellitus*
- *Chronic kidney disease, including those that are on dialysis*
- *Chronic liver disease*
- *Immunocompromised patients (including individuals with rheumatoid arthritis, HIV/AIDS and systemic lupus erythematosus)*

As there is insufficient data supporting one dose over another, the Taskforce recommends that the most frequently used dose across studies (1200 mg) should be administered within 7 days of onset of symptoms.

The efficacy of casirivimab plus imdevimab in vaccinated or immunocompromised patients with mild or asymptomatic COVID-19 is not known.

As of 29 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.3 Systemic corticosteroids

6.1.3.1 Corticosteroids for adults

Recommended

Use dexamethasone 6 mg daily intravenously or orally for up to 10 days (or acceptable alternative regimen) in **adults with COVID-19 who are receiving oxygen** (including mechanically ventilated patients).

The suggested regimen of corticosteroid use is 6 mg of dexamethasone (oral or intravenous) daily for up to 10 days. In patients for whom dexamethasone is not available, acceptable alternative regimens include:

- *hydrocortisone: intravenous (50 mg), every 6 hours for up to 10 days*
- *prednisolone: oral (50 mg), daily for up to 10 days*
- *methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain*

It is unclear whether older people living with frailty or cognitive impairment, or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

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

Corticosteroids may still be considered for other evidence-based indications in people who have COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.4 Other immunomodulating drugs

6.1.4.1 Baricitinib

6.1.4.1.1 Baricitinib for adults

Conditional recommendation

Updated

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

In patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for baricitinib both within and outside the context of a randomised trial.

In accordance with the ACTT-2 and COV-BARRIER studies, baricitinib should be administered as a 4 mg oral daily dose for up to 14 days. In patients receiving more intensive oxygen delivery where oral administration is not feasible, administer via nasogastric tube. Consider using a reduced dose of 2 mg daily in patients with an eGFR of between 30 and 60 mL/min/ 1.73m2.

The Taskforce previously recommended baricitinib for use in patients who required supplemental oxygen but not mechanical ventilation or ECMO due to the absence of direct evidence within this population. Data from the COV-BARRIER extension study suggests baricitinib is safe and effective in patients hospitalised with COVID-19 who require mechanical ventilation or ECMO. The Taskforce has subsequently revised the recommendation to include these patients

*The Taskforce notes the current **critical shortage of tocilizumab**. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click here.*

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.4.2 Sarilumab

6.1.4.2.1 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.

In patients hospitalised with COVID-19 who require high-flow oxygen, non-invasive ventilation or invasive mechanical ventilation, sarilumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for sarilumab both within and outside the context of a randomised trial.

Uncertainty remains whether sarilumab impacts mortality in patients who require no ventilatory support or low-flow oxygen.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.1.4.3 Tocilizumab

6.1.4.3.1 Tocilizumab for adults

Conditional recommendation

Updated

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

In patients hospitalised with COVID-19 who require supplemental oxygen, tocilizumab probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for tocilizumab both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

*The Taskforce notes the current **critical shortage of tocilizumab**. Therefore, in patients who are receiving supplemental oxygen, baricitinib should be considered as an alternative to tocilizumab, unless contraindicated. For the TGA and Medicine Availability Working Group statements regarding the shortage, click here.*

In accordance with the RECOVERY trial, tocilizumab should be administered as a single intravenous infusion over 60 minutes. The suggested dose is dependent on body weight:

- *Patients > 90 kg: 800 mg tocilizumab*
- *Patients 66–90 kg: 600 mg tocilizumab*
- *Patients 41–65 kg: 400 mg tocilizumab*
- *Patients ≤ 40 kg: 8 mg/kg tocilizumab*

In the RECOVERY trial, 29% of patients received a second dose 12-24 hours after the first dose, although results were not reported separately for this population. The decision to administer a second dose of tocilizumab should take into consideration its availability.

In addition, the RECOVERY and REMAP-CAP trials have demonstrated a significant benefit when using corticosteroids in conjunction with tocilizumab. Use of combined tocilizumab and corticosteroids should be considered in patients hospitalised with COVID-19 who require oxygen, however the optimal sequencing of tocilizumab and corticosteroid use is unclear.

As tocilizumab inhibits the production of C-reactive protein (CRP), a reduction in CRP should not be used as a marker of clinical improvement.

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

6.1.5 Remdesivir

6.1.5.1 Remdesivir for adults

Conditional recommendation

Consider using remdesivir for adults hospitalised with moderate to severe COVID-19 who do not require ventilation.

In patients hospitalised with COVID-19 who do not require ventilation (invasive or non-invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)) remdesivir probably reduces the risk of death. Because of this, the Taskforce gives a conditional recommendation for remdesivir both within and outside the context of a randomised trial.

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

We are aware of the difference between our recommendations for remdesivir and those currently issued by the World Health Organization [51]. For a full description of the rationale underpinning this decision please see here.

It is unclear which regimen of remdesivir (5-day or 10-day) provides the optimal duration of treatment. In Australia, criteria for accessing remdesivir from the National Medical Stockpile limits the treatment course to 5 days for eligible patients.

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

Not recommended

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

Remdesivir should be continued with the appropriate dose and duration, if it was started prior to requiring ventilation.

Within this population, ventilation includes invasive or non-invasive mechanical ventilation and extracorporeal membrane oxygenation (ECMO).

It is unclear whether older people or those requiring palliative care were included in the studies this recommendation is based on. Until further evidence in these populations is available, the Taskforce does not believe a different recommendation should apply, unless contraindicated.

Use of remdesivir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include remdesivir.

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

6.1.6 Sotrovimab

6.1.6.1 Sotrovimab for adults

Conditional recommendation

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

Please note: The Taskforce has made additional recommendations on the use of sotrovimab in immunosuppressed and fully vaccinated patients. These are available below.

In patients with confirmed COVID-19 who do not require oxygen, sotrovimab probably decreases the risk of hospitalisation if taken within 5 days of onset of symptoms.

Results are based on the COMET-ICE trial [620], in which non-vaccinated adults were treated with a single one-hour intravenous infusion of 500 mg sotrovimab. Based on the inclusion criteria for this trial, risk factors for disease progression include the following:

- *Diabetes (requiring medication)*
- *Obesity (BMI > 30 kg/m2)*
- *Chronic kidney disease (i.e. eGFR < 60 by MDRD)*
- *Congestive heart failure (NYHA class II or greater)*
- *Chronic obstructive pulmonary disease (history of chronic bronchitis, chronic obstructive lung disease, or emphysema with dyspnoea on physical exertion)*
- *Moderate-to-severe asthma (requiring an inhaled steroid to control symptoms or prescribed a course of oral steroids in the previous 12 months)*
- *Age ≥ 55 years*

Pregnant & breastfeeding women and children & adolescents were not included in the trial. However trials are underway in which children over 12 years of age are eligible for inclusion (OPTIMISE-C19, NCT04913675).

The efficacy of sotrovimab in vaccinated or immunocompromised patients is unknown.

As of 28 October 2021, the Taskforce has made conditional recommendations supporting the use of both sotrovimab and casirivimab plus imdevimab in adult outpatients with mild or asymptomatic COVID-19. As there is no evidence directly comparing sotrovimab to casirivimab plus imdevimab, it is unclear if one treatment is more effective than the other.

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

Consensus recommendation

Within the patient population for which 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 age or multiple risk factors, and COVID-19 vaccination status.

Consider using sotrovimab in unvaccinated or partially vaccinated patients and patients who are immunosuppressed regardless of vaccination status.

Do not routinely use sotrovimab in fully vaccinated patients unless immunosuppressed.

The available research does not currently provide enough evidence to determine the benefits of sotrovimab in specific subgroups of patients. In the absence of definitive evidence, the Taskforce has arrived at a consensus recommendation based on their combined clinical expertise to guide clinical decisions about which patients are most likely to benefit from sotrovimab.

There is no evidence evaluating the effectiveness of sotrovimab in fully vaccinated patients, a low likelihood of development of severe disease, and a small risk of adverse events. Given this and the lower risk of deterioration in these patients, it is unlikely that sotrovimab will be particularly valuable in fully vaccinated patients, unless the patient is immunosuppressed.

There are is no evidence on the effectiveness of sotrovimab in immunosuppressed patients. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that sotrovimab will be beneficial for immunosuppressed patients.

Immunocompromising conditions include:

- *Primary or acquired immunodeficiency*
  - *Haematologic neoplasms: leukaemias, lymphomas, myelodysplastic syndromes*
  - *Post-transplant: solid organ (on immunosuppressive therapy), haematopoietic stem cell transplant (within 24 months)*
  - *Immunocompromised due to primary or acquired (HIV/AIDS) immunodeficiency*
  - *Other significantly immunocompromising conditions*
- *Immunosuppressive therapy (current or recent)*
  - *Chemotherapy or radiotherapy*
  - *High-dose corticosteroids (≥ 20 mg of prednisone per day, or equivalent) for ≥ 14 days*
  - *All biologics and most disease-modifying anti-rheumatic drugs (DMARDs) [553]*

6.2 Disease-modifying treatments that are not recommended

6.2.1 Aspirin

Not recommended

Do not use aspirin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of aspirin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include aspirin.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.2.2 Azithromycin

Not recommended

Do not use azithromycin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of azithromycin may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include azithromycin.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.3 Colchicine

Not recommended

Updated

Do not use colchicine for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of colchicine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include colchicine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.4 Convalescent plasma

Not recommended

Do not use convalescent plasma for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of convalescent plasma may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include convalescent plasma.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.5 Hydroxychloroquine

Not recommended

Updated

Do not use hydroxychloroquine for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of hydroxychloroquine may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include hydroxychloroquine.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.6 Hydroxychloroquine plus azithromycin

Not recommended

Do not use hydroxychloroquine plus azithromycin for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither hydroxychloroquine nor azithromycin as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

6.2.7 Interferon β-1a

Not recommended

Do not use subcutaneous or intravenous interferon β-1a for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of subcutaneous or intravenous interferon β-1a may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include interferon β-1a.

Information regarding the use of inhaled interferon β-1a for the treatment of COVID-19 can be found here.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.8 Interferon β-1a plus lopinavir-ritonavir

Not recommended

Do not use intravenous interferon β-1a plus lopinavir-ritonavir for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Although certainty of the evidence is low, this recommendation is supported by the observation that neither intravenous interferon β-1a nor lopinavir-ritonavir as standalone treatments demonstrate a benefit when administered to patients with COVID-19.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

6.2.9 Lopinavir-ritonavir

Not recommended

Do not use lopinavir-ritonavir for the treatment of COVID-19.

This recommendation applies to adults, children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care.

Use of lopinavir-ritonavir may still be considered in the context of randomised trials with appropriate ethical approval, such as combination therapies that include lopinavir-ritonavir.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

8. Respiratory support in adults

Consensus recommendation

Guiding principles of care

For patients with COVID-19 receiving respiratory support (CPAP/HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms, or administer these therapies in wards where patients are confirmed COVID-19 positive. Healthcare workers should ensure they wear appropriate personal protective equipment, ensuring personal contact, eye protection, droplet and airborne precautions are in place. Healthcare workers should be fully vaccinated.

The additional relative risk of infection to healthcare workers associated with specific oxygen therapies and respiratory support is uncertain but is thought to add minimal additional risk in an environment where transmission of infection with COVID-19 is already high.

8.1 Continuous positive airway pressure / High-flow nasal oxygen therapy

Info Box

When caring for patients with COVID-19, pneumonia clinicians need to determine an SpO2 target range for when oxygen therapies are required. The target ranges are:

- 92–96% in most patients
- 88–92% in patients at risk of hypercapnia

Conventional oxygen therapy can be delivered by nasal prongs or Venturi masks. Deliver oxygen at 1–4 L/min to maintain SpO2 within the desired target range.

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen that is humidified and heated, via large diameter nasal cannula. Flow rates can be given from 40 L/min up to 60 L/min with an oxygen/air blender supplying oxygen at 21–100%.

Continuous positive airway pressure (CPAP) is the non-invasive application of positive end expiratory pressure (with or without entrained oxygen). It can aid in alveolar recruitment and optimise oxygen delivery.

Conditional recommendation

Consider using continuous positive airway pressure (CPAP) therapy for patients with persistent hypoxaemia (defined as requiring an FiO2 ≥ 0.4 to maintain SpO2 in their target range) associated with COVID-19. Adjust positive end-expiratory pressure as required, most patients require pressures of 10 to 12 cm. Excessive pressures may increase the risk of pneumothorax. Adjust oxygen to maintain SpO2 in the target range, FiO2 0.4 to 0.6.

Patients requiring CPAP for COVID-19 pneumonia are at high risk of further deterioration, requiring intubation and mechanical ventilation. Liaise with ICU and monitor closely for deterioration.

If CPAP is not available or not tolerated, consider HFNO as an alternative using the same safety parameters as CPAP.

Use the lowest flow necessary to maintain oxygen saturation ≥ 92%.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.2 Non-invasive ventilation

Info Box

Non-invasive ventilation (NIV), also known as non-invasive positive pressure ventilation (NIPPV) or bilevel positive pressure support (BiPAP), is a form of respiratory support. Bilevel positive pressure is delivered throughout the respiratory cycle by a firm-fitting nasal-face mask. The patient breathes spontaneously and triggers the device to cycle.

A higher level of pressure is provided during the inspiratory phase to enhance ventilation, while a lower level of continuous positive pressure is delivered during the expiratory phase (also known as positive end-expiratory pressure or PEEP). Supplemental oxygen can also be delivered through the device.

Conditional recommendation

Consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety including the use of appropriate personal protective equipment (PPE). If NIV is being used, ideally this should be in a negative pressure room. If none is available, other alternatives are single rooms, or shared ward spaces with cohorting of confirmed COVID-19 patients only.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient's expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Conditional recommendation

In patients with COVID-19 for whom NIV is appropriate for an alternate clinical presentation (e.g. concomitant chronic obstructive pulmonary disease (COPD) with type 2 respiratory failure and hypercapnia, acute pulmonary oedema), ensure airborne and other infection control precautions are optimised.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient's expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.3 Respiratory management of the deteriorating patient

Consensus recommendation

Do not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised, less invasive respiratory therapies.

Patients can deteriorate rapidly 5 to 10 days after onset of symptoms.

The net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and an advance care directive or plan if available, and consideration of the patient's expected short- and long-term responses to more invasive forms of treatment.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.4 Videolaryngoscopy

Conditional recommendation

In adults with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.5 Neuromuscular blockers

Info Box

Neuromuscular blocking agents (NMBAs) are a pharmaceutical intervention that may facilitate protective lung ventilation in patients who are mechanically ventilated with moderate to severe acute respiratory distress syndrome (ARDS). NMBAs may reduce patient-ventilator dyssynchrony and facilitate improved oxygenation by various mechanisms, including reducing the inspiratory muscle effort and the work of breathing, and reducing ventilator-induced lung injury.

Conditional recommendation against

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, do not routinely use continuous infusions of neuromuscular blocking agents (NMBAs).

However, if protective lung ventilation cannot be achieved, consider using NMBAs for up to 48 hours. If indicated, consider cisatracurium as first-line agent, if cisatracurium is not available alternatives include atracurium or vecuronium by infusion.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.6 Positive end-expiratory pressure

Consensus recommendation

For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, consider using a higher PEEP strategy (PEEP > 10 cm H2O) over a lower PEEP strategy.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.7 Prone positioning

Info Box

Positioning the patient in a face-down (prone) position may help to open up (recruit) collapsed alveoli and improve oxygen levels in the blood.

8.7.1 Prone positioning for adults

Consensus recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning for more than 12 hours a day.

Current reports suggest prone ventilation is effective in improving hypoxia associated with COVID-19. This should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events, e.g. accidental extubation.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

Conditional recommendation

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning for at least 3 hours per day as tolerated. When positioning a patient in prone, ensure proning is used with caution and accompanied by close monitoring of the patient. Use of prone positioning should not delay endotracheal intubation and mechanical ventilation in patients with COVID-19 who are deteriorating despite optimised less invasive respiratory therapies.

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, prone positioning for as long as tolerated (ideally 8 hours or more) is likely to increase benefits.

Vulnerable people who are treated outside the ICU, for example people who are older and living with frailty, cognitive impairment or unable to communicate, may especially be at increased risk of harm from proning. Despite the potential risks of awake proning associated with frailty, there may be benefits for this group. The net clinical benefit for each individual patient should be considered on a case-by-case basis.

Currently, the evidence indicates that prone positioning probably decreases treatment failure and the need for intubation, with no increase in harms. Prone positioning should be done in the context of a hospital guideline that includes suitable personal protective equipment (PPE) for staff and which minimises the risk of adverse events.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.8 Recruitment manoeuvres

Info Box

Patients receiving respiratory support are at an increased risk of lung injury. Recruitment manoeuvres are used to open up ('recruit') collapsed alveoli and are a common element of an 'open lung approach' to protect the lungs during mechanical ventilation. The manoeuvres use a sustained increase in airway pressure to re-open collapsed alveoli.

Types of manoeuvres include: prolonged high continuous positive airway pressure; progressive incremental increases in positive end-expiratory pressure at a constant driving pressure (incremental PEEP, stepwise or staircase); and high driving pressures.

Consensus recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider using recruitment manoeuvres.

If recruitment manoeuvres are used, do not use staircase or stepwise (incremental PEEP) recruitment manoeuvres.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

8.9 Extracorporeal membrane oxygenation

Info Box

Extracorporeal membrane oxygenation (ECMO) is a form of life support that removes blood from the body via large cannulae, oxygenates and removes carbon dioxide from the blood external to the patient, and then returns the blood to the body.

Venovenous (VV) ECMO provides oxygenation support for the lungs only, while venoarterial (VA) ECMO supports the heart and lungs.

8.9.1 ECMO for adults

Conditional recommendation

Consider early referral to an ECMO centre for patients developing refractory respiratory failure in mechanically ventilated adults with COVID-19 (despite optimising ventilation, including proning and neuromuscular blockers).

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected patients with COVID-19 and severe ARDS.

Net clinical benefit for each patient should be considered on a case-by-case basis, as factors such as frailty, advanced illness or comorbidity may lessen the benefit and increase potential harms.

Decisions around proceeding to more invasive forms of therapy should consider the preferences and values of the patient and whether they have an advanced care directive or plan, and should be discussed with the patient or their substitute / medical treatment decision-maker.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9. Respiratory support in neonates, children and adolescents

9.1 Requiring non-invasive respiratory support

9.1.1 High-flow nasal oxygen and non-invasive ventilation

Info Box

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where warmed, humidified oxygen is delivered at high-flow rates.

Non-invasive ventilation (NIV) refers to any type of positive pressure support delivered without an endotracheal tube during spontaneous breathing. Supplemental oxygen can also be delivered through the device.

HFNO or NIV should be considered when low-flow oxygen is unable to maintain target peripheral oxygen saturation and/or to treat respiratory distress. Target peripheral oxygen saturations may vary in neonates, children and adolescents with co-morbid conditions, such as preterm birth, cyanotic congenital heart disease or chronic lung disease.

Consensus recommendation

Consider using high-flow nasal oxygen (HFNO) or non-invasive ventilation (NIV) therapy for neonates, children and adolescents with hypoxaemia or respiratory distress associated with COVID-19 and not responding to low-flow oxygen. Use it with caution and pay strict attention to staff safety, including the use of appropriate PPE.

The preferred location for high-flow nasal oxygen is a negative pressure room or a single room with the door closed. If these locations are not immediately available then HFNO or NIV should not be withheld if indicated. However, it should be recognised that this therapy may pose an aerosol risk to staff and other patients, and appropriate precautions should be used.

In children and adolescents with COVID-19 for whom HFNO or NIV is appropriate for an alternate clinical presentation (e.g. concomitant bronchiolitis or severe asthma), ensure airborne and other infection control precautions are also optimised.

Consider early transfer in the deteriorating neonate, child or adolescent to a specialised paediatric or neonatal critical care unit.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2 Requiring invasive mechanical ventilation

9.2.1 Prone positioning (mechanical ventilation)

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning if there are no contraindications.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.2 Positive end-expiratory pressure (PEEP)

Consensus recommendation

For mechanically ventilated neonates, children and adolescents with COVID-19 and moderate to severe ARDS with atelectasis, consider using a higher PEEP strategy over a lower PEEP strategy. The absolute PEEP values that constitute a high and low PEEP strategy will depend on age and patient size.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.5 High-frequency oscillatory ventilation (HFOV)

Info Box

High-frequency oscillatory ventilation (HFOV) is a specialised mode of respiratory support via an endotracheal tube that delivers very small tidal volumes at a rate much faster than normal breathing rates (> 2 Hz). It is used as a rescue therapy in neonates and children for severe respiratory failure when conventional mechanical ventilation is not effective. In neonates with severe respiratory failure, HFOV reduces need for ECMO. HFOV requires specialist equipment, and nursing and medical expertise.

Consensus recommendation

Do not routinely use HFOV as a first line mode of mechanical ventilation in neonates, children and adolescents with severe COVID-19. HFOV should be limited to a rescue therapy in neonates and children not responding to conventional mechanical ventilation in a specialist centre with experience with HFOV.

HFOV delivers gas at very high flow rates. This may increase the aerosol-generating potential compared to other forms of respiratory support used in intensive care. This may limit the suitability of HFOV in patients with COVID-19 unless strict attention to staff safety and infection control measures can be applied.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.6 Videolaryngoscopy

Conditional recommendation

In neonates, children and adolescents with COVID-19 undergoing endotracheal intubation, consider using videolaryngoscopy over direct laryngoscopy if available and the operator is trained in its use.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

9.2.7 Extracorporeal membrane oxygenation (ECMO)

Consensus recommendation

Consider early referral to an ECMO centre for venovenous or venoarterial ECMO in mechanically ventilated neonates, children and adolescents with COVID-19 with refractory respiratory or cardiovascular failure despite optimising other critical care interventions.

Due to the resource-intensive nature of ECMO and the need for experienced centres, healthcare workers and infrastructure, ECMO should only be considered in selected neonates, children and adolescents with severe or critical COVID-19 and no contraindications for ECMO, such as severe, irreversible organ dysfunction.

The decision on whether to use ECMO should be taken in consultation with the child's family. Key considerations include pre-existing conditions and the suitability of anticoagulation.

Early referral to an ECMO centre is preferred.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

10. Venous thromboembolism (VTE) prophylaxis

10.1 VTE prophylaxis for adults

Conditional recommendation

Use prophylactic doses of anticoagulants, preferably low molecular weight heparin (LMWH) (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily), in **adults with moderate, severe or critical COVID-19 or other indications**, unless there is a contraindication, such as risk for major bleeding. Where the estimated glomerular filtration rate (eGFR) (see below) is less than 30 mL/min/1.73m2, unfractionated heparin or clearance-adjusted doses of LMWH may be used (e.g. enoxaparin 20 mg once daily).

For body weights outside 50–90 kg or heights outside 150–180 cm, calculate the body surface area (BSA) and multiply the eGFR by BSA/1.73.

The Taskforce notes that in critical illness, creatinine-based estimation of kidney function can be unreliable.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Conditional recommendation against

Do not routinely offer therapeutic anticoagulant dosing in adults with moderate, severe or critical COVID-19. There is no additional indication for therapeutic dosing for anticoagulants in adults with severe or critical COVID-19 beyond current standard best practice.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

10.2 VTE prophylaxis for pregnant and postpartum women

Info Box

Pregnant women in general are at an increased risk of venous thromboembolism (VTE). Hospitalised pregnant women with an acute infective illness (such as COVID-19) are at even greater risk of VTE. However, the exact duration of increased risk of VTE in association with COVID-19 infection is not yet established.

All pregnant and postpartum women should undergo a documented assessment of risk factors for VTE on admission to hospital, if COVID-19 is diagnosed, if COVID-19 severity changes and postpartum.

The use of pharmacological prophylaxis in women should be accompanied by other measures to prevent VTE, such as anti-embolism stockings and sequential compression devices.

Consensus recommendation

For pregnant or postpartum women who are admitted to hospital (for any indication) and who have COVID-19, use prophylactic doses of anticoagulants, preferably LMWH (e.g. enoxaparin 40 mg once daily or dalteparin 5000 IU once daily) unless there is a contraindication, such as risk for major bleeding or imminent birth.

Prophylactic anticoagulants should be continued for at least 14 days after discharge or until COVID-19-related morbidity (including immobility, dehydration and/or shortness of breath) has resolved.

- *Dosing of LMWH is dependent on pre-pregnancy body weight and current renal function.*
- *For women with early pregnancy body weight outside of 50–90 kg, consider adjusted LMWH dosing.*
- *There is limited evidence to guide the most appropriate dose in obese patients but standard dosing may be inadequate.*

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11. Therapies for existing indications in patients with COVID-19

11.1 ACEIs/ARBs in patients with COVID-19

Recommended

In patients with COVID-19 who are receiving ACEIs/ARBs, there is currently no evidence to deviate from usual care and these medications should be continued unless contraindicated.

Stopping these medications abruptly can lead to acute heart failure or unstable blood pressure.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11.3 Steroids for people with asthma or COPD with COVID-19

Consensus recommendation

Use inhaled or oral steroids for the management of people with co-existing asthma or chronic obstructive pulmonary disease (COPD) and COVID-19 as you would normally for viral exacerbation of asthma or COPD. Do not use a nebuliser.

This is a low priority recommendation and we do not expect to update it in the immediate future, however we continue to conduct daily searches for new evidence.

11.4 Oestrogen-containing therapies

Consensus recommendation

Consider stopping oral menopausal hormone therapy (MHT), also known as hormone replacement therapy (HRT), in women with **mild or moderate COVID-19**.

Before restarting oral MHT, review the indication for this. If MHT is continued, consider using a transdermal preparation.

Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Consensus recommendation

Stop oral menopausal hormone therapy (MHT) in women with **severe or critical COVID-19**.

Before restarting oral MHT, review the indication for this and consider transitioning to a transdermal preparation.

Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

Consensus recommendation

In women who have COVID-19 and who are taking oestrogen-containing contraception, manage these medications as per usual care.

In women who stop or suspend contraception when they have COVID-19, restart contraception at the time of discharge or when acute symptoms have resolved.

Decisions around stopping hormone therapy should be discussed with the patient or their substitute / medical treatment decision-maker. The goals of patient care need to balance the preferences and values of the patient, based on discussion and consideration of the patients individual circumstances.

This is a moderate priority recommendation and will be updated when new evidence becomes available that is likely to impact the direction or strength of the recommendation.

WHO, 2021 [20].

World Health Organization (WHO)

Therapeutics and COVID-19: living guideline; WHO/2019-nCoV/therapeutics/2021.3.

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: 24.09.2021

LoE/GoR

- GRADE methodology

Recommendations for therapeutics

7.1 Casirivimab and imdevimab (neutralizing monoclonal antibodies)

For patients with non-severe COVID-19 (who do not meet criteria for severe or critical infection)

Conditional recommendation — New

We suggest treatment with casirivimab and imdevimab, conditional to those at highest risk of hospitalization.

- *Whereas casirivimab and imdevimab achieves a substantial reduction in the relative risk of hospitalization, the absolute benefit will be trivial or unimportant 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 and 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

New

We suggest treatment with casirivimab and imdevimab, under the condition that the patient has seronegative status.

- *With benefits of casirivimab and 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 and imdevimab is in addition to the current standard of care, which includes corticosteroids and IL-6 receptor blockers.*

7.2. IL-6 receptor blockers

Recommended

New

We recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) for patients with severe or critical COVID-19 infection.

Corticosteroids have previously been strongly recommended in patients with severe and critical COVID-19 (4), and we recommend patients meeting these severity criteria should now receive both corticosteroids and IL-6 receptor blockers.

7.3 Ivermectin (published 31 March 2021)

Only in research settings

We recommend not to use ivermectin in patients with COVID-19 except in the context of a clinical trial.

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.

7.4 Hydroxychloroquine (published 17 December 2020)

Recommendation against

We recommend against administering hydroxychloroquine or chloroquine for treatment of COVID-19.

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

7.5 Lopinavir/ritonavir (published 17 December 2020)

Recommendation against

We recommend against administering lopinavir/ritonavir for treatment of COVID-19.

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

7.6 Remdesivir (published 20 November 2020)

Conditional recommendation against

We suggest against administering remdesivir in addition to usual care.

Practical info

The GDG made a conditional recommendation against using remdesivir for treatment of hospitalized patients with COVID-19. If administration of remdesivir is considered, it should be noted that its use is contraindicated in those with liver (ALT > 5 times normal at baseline) or renal (eGFR < 30 mL/minute) dysfunction. To date, it can only be administered intravenously, and it has relatively limited availability.

7.7 Systemic corticosteroids (published 2 September 2020)

Patients with severe and critical COVID-19

Recommended

Updated evidence, no change in recommendation

We recommend systemic corticosteroids rather than no corticosteroids.

For patients with non-severe COVID-19 infection (absence of criteria for severe or critical infection)

Conditional recommendation against

Updated evidence, no change in recommendation

We suggest not to use corticosteroids.

National Institute for Health and Care Excellence (NICE), 2021 [14].

COVID-19 rapid guideline: managing COVID-19; version 14.0

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. At the time of publication (March 2021), no specific literature searches were carried out for the therapeutics section of the guideline.
- The use of evidence provided by the National Australian COVID-19 clinical evidence taskforce is achieved through the sharing of RevMan files, which the NICE team use to populate the evidence summary section and GRADE profiles for a review.
- Letzte Aktualisierung: 28.10.2021

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.

7 Therapeutics for COVID-19

7.1 Corticosteroids

Strong recommendation

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.

Being on a hospital-supervised virtual COVID ward is not classed as being discharged from hospital.

Dosage in adults

Dexamethasone

- 6 mg orally once a day for 10 days (three 2 mg tablets or 15 ml of 2 mg/5 ml oral solution) or
- 6 mg intravenously once a day for 10 days (1.8 ml of 3.3 mg/ml ampoules [5.94 mg])

For people able to swallow and in whom there are no significant concerns about enteral absorption, prescribe tablets. Only use intravenous administration when tablets or oral solutions are inappropriate or unavailable.

Suitable alternatives

Prednisolone Prednisolone: 40 mg orally once a day for 10 days

Hydrocortisone Hydrocortisone: 50 mg intravenously every 8 hours for 10 days (0.5 ml of 100 mg/ml solution; powder for solution for injection or infusion is also available); this may be continued for up to 28 days for people with septic shock.

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.

7.2 Casirivimab and imdevimab - hospital use

Recommendation

Offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19 who have no detectable SARS-CoV-2 antibodies (seronegative).

The criteria for accessing casirivimab and imdevimab in the UK, and dosage to be used, are outlined in NHS England's Interim Clinical Commissioning Policy on casirivimab and imdevimab for patients hospitalised due to COVID-19 (aged 12 years and above), published in September 2021. The policy states that patients must meet all of the eligibility criteria and none of the exclusion criteria to be given casirivimab and imdevimab.

Not recommended

Do not offer a combination of casirivimab and imdevimab to people aged 12 and over in hospital with COVID-19:

- who have detectable SARS-CoV-2 antibodies (seropositive), or
- whose serostatus is unknown.

7.3 Remdesivir

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Low-flow oxygen supplementation: oxygen delivered by a simple face mask or nasal canula at a flow rate usually up to 15 litres/min.

Conditional recommendation

Consider remdesivir for up to 5 days for COVID-19 pneumonia in adults, and young people 12 years and over weighing 40 kg or more, in hospital and needing low-flow supplemental oxygen.

The criteria for accessing remdesivir in the UK are outlined in NHS England's Interim Clinical Commissioning Policy on remdesivir for patients hospitalised with COVID-19 (adults and children 12 years and older), which was updated in June 2021 to include eligibility criteria for remdesivir in people who are significantly immunocompromised.

For remdesivir use in pregnancy, follow the Royal College of Obstetrics and Gynaecology guidance on coronavirus (COVID-19) infection and pregnancy.

The marketing authorisation for remdesivir for COVID-19 does not include children under 12 years or weighing less than 40 kg.

Only in research settings

Do not use remdesivir for COVID-19 pneumonia in adults, young people and children who are 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.

7.4 Tocilizumab

Definition

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Strong recommendation

Offer tocilizumab to adults in hospital with COVID-19 if all of 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.

In October 2021, the marketing authorisations for tocilizumab do not cover use in COVID-19. See NICE's information on prescribing medicines for more about off-label and unlicensed use

of medicines. The recommended dosage for tocilizumab is a single dose of 8 mg/kg by intravenous infusion. The total dose should not exceed 800 mg.

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.

7.5 Sarilumab

Conditional recommendation

Consider sarilumab for adults in hospital with COVID-19 if tocilizumab cannot be used or is unavailable. Use the same eligibility criteria as those for tocilizumab. That is, if all of 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.

In October 2021, the marketing authorisations for sarilumab do not cover use in COVID-19. The recommended dosage for sarilumab is a single dose of 400 mg by intravenous infusion.

7.6 Low molecular weight heparins

For recommendations on the therapeutic use of low molecular weight heparins, see the section on venous thromboembolism (VTE) prophylaxis.

7.7 Vitamin D supplementation

For recommendations on vitamin D, see the NICE COVID-19 rapid guideline on vitamin D.

7.8 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.

See also the recommendations on azithromycin and doxycycline in the section on therapeutics for COVID-19.

7.9 Azithromycin

Not recommended

Do not use azithromycin to treat COVID-19.

7.10 Colchicine

Not recommended

Do not offer colchicine to people in hospital to treat COVID-19.

NICE is aware that there is newly published evidence on colchicine from the RECOVERY trial and this is being reviewed.

Only in research settings

Only use colchicine to treat COVID-19 in community settings as part of a clinical trial.

7.11 Doxycycline

Not recommended

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

8.3 Venous thromboembolism (VTE) prophylaxis

Definitions

Invasive mechanical ventilation: any method of controlled ventilation delivered through a translaryngeal or tracheostomy tube, or other methods as defined by the Intensive Care National Audit & Research Centre definition of 'advanced respiratory support'.

Hospital-led acute care in the community: a setting in which people who would otherwise be admitted to hospital have acute medical care provided by members of the hospital team, often working with the person's GP team. They include hospital at home services and COVID-19 virtual wards.

Standard prophylactic dose: the prophylactic dose of a low molecular weight heparin (LMWH), as listed in the medicine's summary of product characteristics, for medical patients.

Intermediate dose: double the standard prophylactic dose of an LMWH for medical patients.

Treatment dose: the licensed dose of anticoagulation used to treat confirmed VTE.

8.3.1 In hospital

Consensus recommendation

For young people and adults with COVID-19 that is being managed in hospital, assess the risk of bleeding as soon as possible after admission or by the time of the first consultant review. Use a risk assessment tool published by a national UK body, professional network or peer-reviewed journal.

Recommended

Offer a standard prophylactic dose of a low molecular weight heparin as soon as possible, and within 14 hours of admission, to young people and adults with COVID-19 who need low-flow or high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation, and who do not have an increased bleeding risk.

Treatment should be continued for a minimum of 7 days, including after discharge.

Conditional recommendation

Consider a treatment dose of a low molecular weight heparin (LMWH) for young people and adults with COVID-19 who need low-flow oxygen and who do not have an increased bleeding risk.

Treatment should be continued for 14 days or until discharge, whichever is sooner. Dose reduction may be needed to respond to any changes in a person's clinical circumstances.

For people with COVID-19 who do not need low-flow oxygen, follow the recommendations in NICE's guideline on venous thromboembolism in over 16s.

In August 2021, using a treatment dose of a LMWH outside the treatment of confirmed VTE was an off-label use of parenteral anticoagulants. See NICE's information on prescribing medicines.

Only in research settings

Only offer an intermediate or treatment dose of a low molecular weight heparin to young people and adults with COVID-19 who are receiving high-flow oxygen, continuous positive airway pressure, non-invasive ventilation or invasive mechanical ventilation as part of a clinical trial.

Consensus recommendation

Do not base prophylactic dosing of heparin on levels of D-dimer.

Consensus recommendation

For people at extremes of body weight or with impaired renal function, consider adjusting the dose of low molecular weight heparins in line with the summary of product characteristics and locally agreed protocols.

Consensus recommendation

For people who cannot have low molecular weight heparins (LMWHs), use fondaparinux sodium or unfractionated heparin (UFH).

In August 2021, LMWHs and fondaparinux sodium were off label for people under 18 years.

Consensus recommendation

For people who are already having anticoagulation treatment for another condition when admitted to hospital:

- continue their current treatment dose of anticoagulant unless contraindicated by a change in clinical circumstances
- consider switching to a low molecular weight heparin (LMWH) if their current anticoagulant is not an LMWH and their clinical condition is deteriorating.

Consensus recommendation

If a person's clinical condition changes, assess the risk of VTE, reassess bleeding risk and review VTE prophylaxis.

Consensus recommendation

Organisations should collect and regularly review information on bleeding and other adverse events in people with COVID-19 having treatment or intermediate doses of pharmacological VTE prophylaxis.

Consensus recommendation

Ensure that people who will be completing pharmacological VTE prophylaxis after discharge are able to use it correctly or have arrangements made for someone to help them.

8.3.2 In hospital-led acute care in the community

Consensus recommendation

For people with COVID-19 managed in hospital-led acute care in the community settings:

- assess the risks of VTE and bleeding
- consider pharmacological prophylaxis if the risk of VTE outweighs the risk of bleeding.

Chalmers JD et al., 2021 [5].

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”.

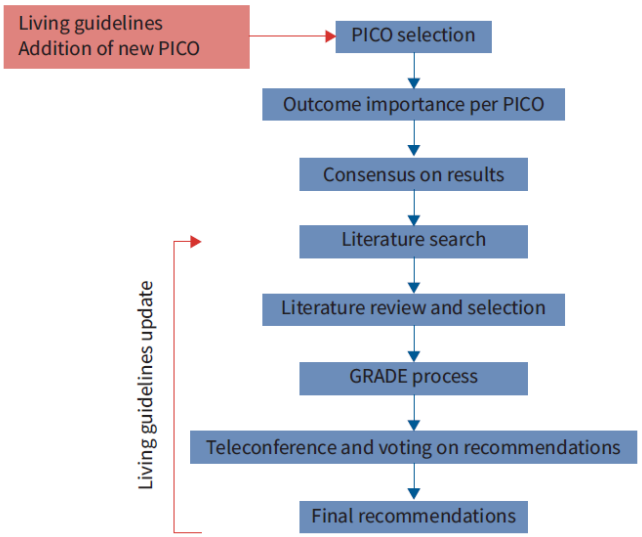


FIGURE 1 Process of guideline development. PICO: population, intervention, comparator, outcome.

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.

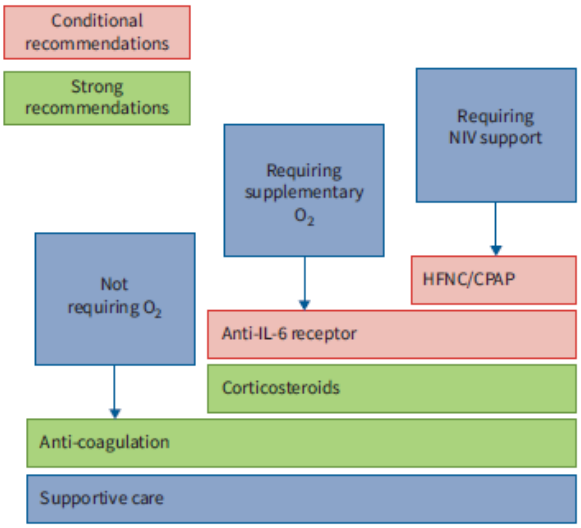


FIGURE 2 Summary of the European Respiratory Society guideline for management of hospitalised patients with coronavirus disease 2019. NIV: noninvasive ventilation; HFNC: high-flow nasal cannula oxygen; CPAP: continuous positive airway pressure; IL: interleukin.

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.

Basetti M et al., 2021 [4].

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 8 of 12, August 2021) am 12.08.2021

#	Suchfrage
1	MeSH descriptor: [COVID-19] explode all trees
2	MeSH descriptor: [SARS-CoV-2] explode all trees
3	MeSH descriptor: [Coronavirus Infections] explode all trees
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 Aug 2016 and Aug 2021

Systematic Reviews in Medline (PubMed) am 12.08.2021

#	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

#	Suchfrage
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 ("2016/08/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT "The Cochrane database of systematic reviews"[Journal]
15	(#14) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 12.08.2021

#	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 ("2016/08/01"[PDAT] : "3000"[PDAT])
14	(#13) NOT (retracted publication [pt] OR retraction of publication [pt])

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Anhang

Ansems K et al., Jahr [3].

Abbildung 2: Ergebnisse RoB2 tool

RISK OF BIAS

Legend: Low risk of bias | High risk of bias | Some concerns

Risk of bias for analysis 1.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	+	+	+	+	+	+
Spinner 2020	+	+	+	+	+	+
Wang 2020	~	+	+	+	+	~
WHO Solidarity Trial Consortium 2021	+	+	+	+	+	+

Risk of bias for analysis 1.2 All-cause mortality at hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
WHO Solidarity Trial Consortium 2021	+	+	+	+	+	+

Risk of bias for analysis 1.3 All-cause mortality (time-to-event)

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 Worsening of clinical status: new need for mechanical ventilation

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Subgroup 1.4.1 WHO 6 to 9 at day 28 (± 1 day), if ≤5 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~
Spinner 2020	✓	✓	~	✗	✓	✗
WHO Solidarity Trial Consortium 2021	✓	✓	~	✓	~	~

Risk of bias for analysis 1.5 Worsening of clinical status: new need for invasive mechanical ventilation

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Subgroup 1.5.1 WHO 7 to 9 at day 28 (± 1 day), if ≤6 at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 1.6 Worsening of clinical status: new need for non-invasive mechanical ventilation or high-flow oxygen

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.6.1 WHO= 6 at day 29, if ≤5 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.7 Worsening of clinical status: new need for oxygen by mask or nasal prongs

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.7.1 WHO= 5 at day 29, if ≤ 4 at baseline						
Beigel 2020	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.8 Viral clearance

	Bias					
Study	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	Overall
Subgroup 1.8.1 Viral clearance at baseline						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.2 Viral clearance at day 3						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.3 Viral clearance at day 7						
Wang 2020	~	✓	✗	✓	✗	✗
Subgroup 1.8.4 Viral clearance at day 14						
Wang 2020	~	✓	✗	✓	✗	✗

Risk of bias for analysis 1.9 Serious adverse events

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	✓	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 1.10 Adverse events, any grade

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	~	✓	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 1.11 Adverse events, grade 3 to 4

Study	Bias					Overall
	Randomisation process	Deviations from intended interventions	Missing outcome data	Measurement of the outcome	Selection of the reported results	
Beigel 2020	✓	~	~	✓	✓	~
Spinner 2020	✓	✓	~	✓	~	~
Wang 2020	~	✓	~	✓	✓	~

Risk of bias for analysis 2.1 All-cause mortality at up to day 28

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Subgroup 2.1.1 Age <50 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 2.1.2 Age 50 to 69 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 2.1.3 Age >69 years						
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 All-cause mortality at up to day 28

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Subgroup 3.1.1 ≤ 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~
Subgroup 3.1.2 > 10 days of symptom onset						
Wang 2020	~	✓	✓	✓	✓	~

Risk of bias for analysis 4.1 All-cause mortality at up to day 28

Study	Bias: Randomisation process	Bias: Deviations from intended interventions	Bias: Missing outcome data	Bias: Measurement of the outcome	Bias: Selection of the reported results	Overall
Subgroup 4.1.1 No oxygen at baseline						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Beigel 2020	✓	✓	✓	✓	✓	✓
Spinner 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓
Subgroup 4.1.2 Low-flow oxygen at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
Subgroup 4.1.3 Mechanical ventilation at baseline						
Beigel 2020	✓	✓	✓	✓	✓	✓
WHO Solidarity Trial Consortium 2021	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 5.1 All-cause mortality at up to day 28

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 5.1.1 5-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓
Subgroup 5.1.2 10-day remdesivir						
Spinner 2020	✓	✓	✓	✓	✓	✓