Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

und

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

Vorgang: 2025-B-127-z Remdesivir

Stand: Juni 2025

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

Remdesivir [zur Behandlung von COVID-19] **Kriterien gemäß 5. Kapitel § 6 VerfO**	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	Beschlüsse über die Nutzenbewertung nach § 35a SGB V im Anwendungsgebiet COVID-19: - Casirivimab/Imdevimab, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 6. Oktober 2022 - Sotrovimab, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 3. November 2022 - Nirmatrelvir/Ritonavir, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 15. Dezember 2022 - Tixagevimab/Cilgavimab, Beschluss über die Nutzenbewertung nach § 35a SGB V vom 20. April 2023
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** (Text aus Fachinformation)
Zu bewertendes Arzneimittel:	
Remdesivir J05AB16 Veklury	„Veklury is indicated for the treatment of coronavirus disease 2019 (COVID-19) in adults and paediatric patients (at least 4 weeks of age and weighing at least 3 kg): • with pneumonia requiring supplemental oxygen (low- or high-flow oxygen or other non-invasive ventilation at start of treatment) • who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19" Kinder und Jugendliche im Alter von mindestens 4 Wochen mit einem Körpergewicht von 3 bis < 40 kg mit einer COVID-19-Erkrankung, die keine zusätzliche Sauerstoffzufuhr benötigen und ein erhöhtes Risiko haben, einen schweren COVID-19-Verlauf zu entwickeln
Behandlung von COVID-19	
– keine	

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie

Vorgang: 2025-B-127-z (Beratung nach § 35a SGB V) Remdesivir

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	27. Mai 2025

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
Covid-19	coronavirus disease 2019
ECMO	extracorpo-real 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
HR	Hazard Ratio
IDSA	Infectious Diseases Society of America
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
NICE	National Institute for Health and Care Excellence
OR	Odds Ratio
RR	Relatives Risiko
SARS-CoV-2	Severe acute respiratory syndrome coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung einer Coronavirus-Krankheit 2019 (COVID-19) bei pädiatrischen Patienten (im Alter von mindestens 4 Wochen und mit einem Gewicht von 3 bis <40 kg), die keinen zusätzlichen Sauerstoff benötigen und bei denen ein erhöhtes Risiko besteht, dass sich eine schwere COVID-19 entwickelt.

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt. Aufgrund der Aktualität der Thematik/des Indikationsbereichs wurde in der Evidenzsynopse ausschließlich Literatur der letzten 2 Jahre betrachtet.

2 Systematische Recherche

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

Der Suchzeitraum der systematischen Literaturrecherche wurde auf die letzten fünf Jahre eingeschränkt und die Recherchen am 05.03.2025 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Auflistung durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherchen ergaben insgesamt 9095 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Dabei wurde für systematische Reviews, inkl. Meta-Analysen, und für Leitlinien ein Publikationszeitraum von 2 Jahren betrachtet. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet.

Vor Fertigstellung der Synopse wurde die Aktualität eingeschlossener Leitlinien geprüft. Nachträglich wurden am 26.05.2025 drei aktualisierte Leitliniendokumente [1,2,5] identifiziert. Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgt eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen

3 Ergebnisse

3.1 Cochrane Reviews

Es wurden keine relevanten Cochrane Reviews identifiziert.

3.2 Systematische Reviews

Es wurden keine relevanten systematischen Reviews identifiziert.

3.3 Leitlinien

Hinweis: Die vorliegenden Leitlinien enthalten generische Empfehlungen für die Behandlung von COVID-19 sowie Empfehlungen und Informationen, die sich spezifisch an Kinder und Jugendliche richten. Empfehlungen für Kinder und Jugendliche werden hervorgehoben.

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Deutsche Gesellschaft für Infektiologie (DGI), 2025 [1,2].

Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)

S3-Leitlinie - Empfehlungen zur Therapie von Patienten mit COVID

Hinweis: Die Leitlinie richtet sich allgemein an Patienten mit COVID-19 und Notwendigkeit der ambulanten und stationären Behandlung. Die Leitlinie enthält den Hinweis, dass die Empfehlungen zur Behandlung einer akuten COVID-19 Infektion im Kindesalter sich v. a. an Studienergebnissen und Erfahrungen aus der Erwachsenenmedizin orientieren, da bisher kaum randomisierten Interventionsstudien für Kinder publiziert wurden. Entsprechend sind keine spezifischen Empfehlungen für die pädiatrische Population in der Leitlinie enthalten.

Zielsetzung/Fragestellung

Management von COVID-19 Patienten.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: **trifft zu**.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**.
- 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:

- Hinweis: Die Leitlinie wird regelmäßig im Sinne einer Living-Guideline aktualisiert. Die aktuelle Version (11.0) ist bis Dezember 2025 gültig. Die Leitlinie wurde erstmals im April 2020 veröffentlicht und zuletzt im Februar 2025 überprüft.

- Im Rahmen der Beantwortung der Schlüsselfrage der Leitlinienaktualisierung: Systematische Recherche nach Kohortenstudien und Fallserien in den Datenbanken MEDLINE und Scopus für den Zeitraum von 2022 bis zum 12.04.2024
- Für die Beantwortung der weiteren Schlüsselfragen, wurde auf den bisherigen Versionen aufgebaut. Eine erfahrene Informationsspezialistin führte systematische Recherchen zu jeder Schlüsselfrage in verschiedenen relevanten Datenbanken ab dem letzten Suchdatum durch. Zunächst wurden per festgelegter Schlüsselfrage gezielt nach randomisiert-kontrollierten Studien recherchiert. Bei mangelnder Studienlage wurden weitere Recherchen zu Observationsstudien ergänzt
- Sofern keine randomisierten-kontrollierten Studien identifiziert werden konnten, wurden nach Möglichkeit aktuelle, qualitativ hochwertige systematische Übersichtsarbeiten herangezogen

Empfehlung	Recherchedatum V1	Recherchedatum V2
Schlüsselfrage 1: Paxlovid und SoC vs. SoC alone	18.10.2023	NA
Schlüsselfrage 2: Remdesivir und SoC vs. Remdesivir alone	09.11.2023	NA
Schlüsselfrage 3: Paxlovid oder Remdesivir vs. SoC alone bei SARS-CoV-2 Viruspersistenz	NA	12.04.2024
Schlüsselfrage 4a: Systemische Kortikosteroide	06.10.2023	NA
Schlüsselfrage 4b: Inhalative Kortikosteroide	06.10.2023	NA
Schlüsselfrage 5: Tocilizumab und SoC vs. SoC	13.10.2023	NA
Schlüsselfrage 6: SARS-CoV-2 spezifische monoklonale Antikörper (Literatur nicht verwendet, da Daten aus in Vitro Studien einen Wirkungsverlust bei jetzigen Varianten aufzeigen)	15.10.2023	NA
Schlüsselfrage 7: Anakinra und SoCvs. SoC alone	11.10.2023	NA
Schlüsselfrage 8: Antikoagulation	25.07.2023	NA
Schlüsselfrage 9: Wachbauchlagerung	09.11.2023	NA

LoE

- GRADE (Einteilung der Qualität der Evidenz in hoch/moderat/niedrig/sehr niedrig)
- Bewertung des Verzerrungsrisikos der einzelnen Studien mit dem Cochrane Risk of Bias 2 Tool für randomisierte Studien bzw. ROBINS I Tool für nichtrandomisierte Studien
- Qualitätsbewertung systematischer Übersichtsarbeiten mit AMSTAR-2

GoR

- 3-stufige Graduierung entsprechend des AWMF-Regelwerks

Symbol	Empfehlungsgrad	Beschreibung	Formulierung
⇑⇑	A	Starke Empfehlung	soll / soll nicht
⇑	B	Empfehlung	sollte / sollte nicht
⇔	0	Empfehlung offen	kann (erwogen werden) / kann (verzichtet werden)

Sonstige methodische Hinweise

Für diese Version der Leitlinie (September 2024) wurde eine Empfehlung zur medikamentösen Kombinationstherapie bei persistierender SARS-CoV-2 Infektion neu formuliert (s. rote Markierung in der entsprechenden Empfehlung).

Empfehlungen

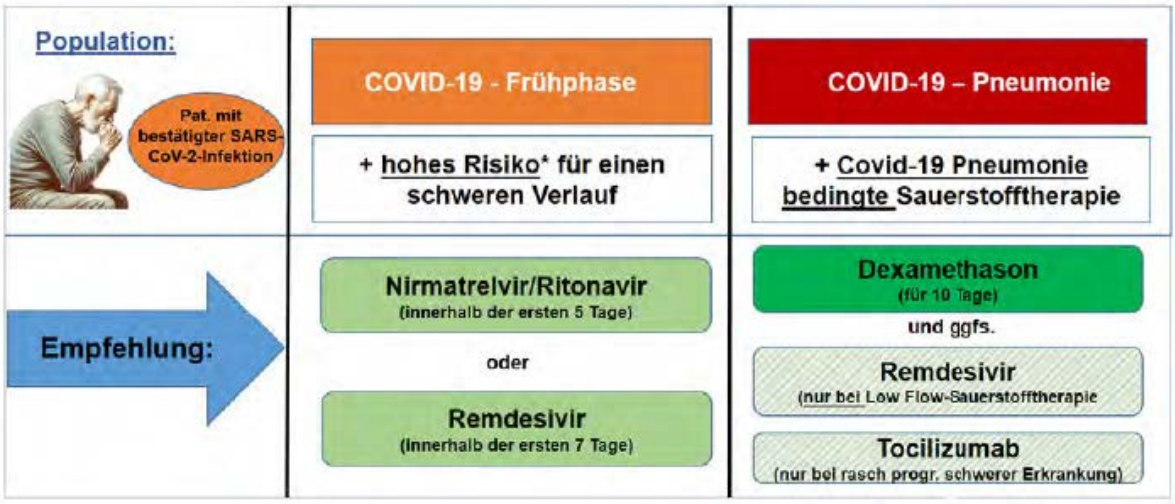
3.3. Spezifische medikamentöse Therapie

Für die medikamentöse Therapie von COVID-19 gibt es antivirale und immunmodulatorische Ansätze, die sich jeweils in den frühen- oder späteren Krankheitsphasen bewährt haben. Diese aktualisierte Version der Leitlinie bezieht auch ambulante Therapien mit ein, welche durch die Verfügbarkeit von wirksamen antiviralen Therapeutika, insbesondere in der Frühphase der Erkrankung, stark an Bedeutung gewonnen haben. Die Frühphase bezieht sich auf die ersten Tage nach dem Auftreten von Symptomen und erstreckt sich je nach Evidenzgrundlage bis zu einem Zeitraum von 5 bis 7 Tagen nach Symptombeginn. Naturgemäß können Patienten aus unterschiedlichen Gründen bereits in der Frühphase mit oder wegen einer SARS-CoV-2-Infektion hospitalisiert sein, sodass eine strikte Unterteilung von ambulanten und stationären Patienten in Bezug auf die Frühphase bei der Evidenzbewertung im Sinne der klinischen Praktikabilität weitgehend vermieden wurde. Im Folgenden sind insbesondere Medikamente aufgeführt, die in einem randomisiert-kontrollierten Studiendesign oder in großen Kohortenstudien untersucht worden sind. Es wurden ausschließlich publizierte Studien nach Peer-Review betrachtet. In der postpandemischen Phase und auf Grundlage der deutlich gesunkenen Fallsterblichkeit favorisiert die Leitliniengruppe derzeit keinen routinemäßigen Off-Label Einsatz von Arzneimitteln zur Therapie der COVID-19-Erkrankung. Vor diesem Hintergrund werden Therapie-Empfehlungen in dieser Aktualisierung ausschließlich für zugelassene Therapeutika ausgesprochen. Aus pragmatischen Gründen wurden Daten zu in Deutschland nicht verfügbaren COVID-19 Arzneimitteln nicht bewertet. Bei der Nutzenbewertung von Therapeutika ist zu beachten, dass Patientenkollektive in klinischen Prüfungen zum Zeitpunkt der Zulassung oft nicht (mehr) der aktuellen Indikationsgruppe entsprechen. Dies betrifft insbesondere die Nutzenwertung von antiviralen Substanzen, die in der Frühphasentherapie eingesetzt werden können, um das Risiko für einen schweren Verlauf mit Krankenhausaufnahme oder Tod zu reduzieren. Aus diesem Grund wurde für antivirale Medikamente teilweise ein Evidenztransfer durchgeführt und nur schwache bzw. offene Empfehlungen für spezielle Risikogruppen ausgesprochen. Die Entscheidung für oder gegen eine antivirale Therapie sollte sich im medizinischen Alltag anhand des individuellen Risikoprofils einschließlich des Immunisierungsstatus und Komorbiditäten orientieren.

3.3.1. Zusammenfassende Empfehlungen

In der COVID-19 Frühphase (innerhalb 1 Woche nach Symptombeginn) sollten Patienten mit hohem Risiko für einen schweren Covid-19 Verlauf antiviral behandelt werden, um dieses Risiko – insbesondere bei ungenügender Immunität - zu reduzieren. Zur Verfügung stehen aktuell Nirmatrelvir/Ritonavir (p.o., 5 Tage Therapiedauer) und Remdesivir (i.v., 3 Tage Therapiedauer). Im Falle einer antiviralen Therapie erfolgt diese als Einzelfallentscheidung unter Einbeziehung von Verfügbarkeit, Kontraindikationen, Hospitalisierungsstatus und individuellem Patientenrisiko. Alle Patienten mit mindestens Low-Flow-Sauerstoff-Bedarf durch eine COVID-19 Pneumonie oder schwererem Erkrankungsverlauf sollen Dexamethason erhalten (WHO Skala 5-9). Bei COVID-19-Pneumonie und Low-Flow-Sauerstoff-Therapie (WHO Skala 5) kann zusätzlich eine antivirale Therapie mit Remdesivir für 5-10 Tage erwogen werden. Ein klinischer Nutzen

einer Therapie mit dem IL-6-Antagonisten Tocilizumab ist nur bei Patienten mit COVID-19-bedingtem Sauerstoffbedarf und rasch progredientem Krankheitsverlauf hin zum respiratorischen Versagen (WHO Skala 5-6) zu erwarten.



Hinweis: Die Grünschattierungen entsprechen der Empfehlungsstärke

3.3.2. Antivirale Therapieansätze

3.3.2.1. Nirmatrelvir/Ritonavir

EMPFEHLUNG 1	**Evidenzbasierte Empfehlung, bestätigt 12/2024**
Empfehlungsgrad: **B ⇑**	**Nirmatrelvir/Ritonavir sollte bei Personen mit einem hohen Risiko für einen schweren Verlauf* in der Frühtherapie (innerhalb der ersten 5 Tage) eingesetzt werden.** Hinweis: Aufgrund des potentiellen Wechselwirkungspotentials sollen relevante Interaktionen mit bestehender Medikation vor Therapiebeginn überprüft und bewertet werden. *hohes Risiko für einen schweren Verlauf = siehe 3.2
Qualität der Evidenz: **Frühphase** 28-Tage-Sterblichkeit: niedrig ⊕⊕⊖⊖ Hospitalisierung/Tod bis Tag 28: niedrig ⊕⊕⊖⊖ Unerwünschte Ereignisse: moderat ⊕⊕⊕⊖	Literatur: Hammond J et al. N Engl J Med. 2022 Feb 16. doi: 10.1056/NEJMoa2118542 Reis S et al. Cochrane Database of Systematic Reviews 2023, Issue 11. Art. No.: CD015395. DOI: 10.1002/14651858.CD015395.pub3
	Starker Konsens

3.3.2.2. Remdesivir

EMPFEHLUNG 2	Evidenzbasierte Empfehlung, bestätigt 12/2024
Empfehlungsgrad: **B ⇑**	**a) Remdesivir sollte bei Personen mit einem hohen Risiko für einen schweren Verlauf* als Frühtherapie (innerhalb von 7 Tagen) eingesetzt werden** *hohes Risiko für einen schweren Verlauf = siehe 3.2
	Ergänzende Empfehlung (EK), bestätigt 12/2024
Expertenkonsens (EK)	**b) Remdesivir kann bei Patienten mit COVID-19 Pneumonie und Low-Flow-Sauerstofftherapie eingesetzt werden**
Qualität der Evidenz: **Frühphase** Hospitalisierung/Tod bis Tag 28: moderat ⊕⊕⊕⊖ **Fortgeschrittene Erkrankung (COVID-19-Pneumonie)** Expertenkonsens	Literatur: Grundeis F et al. Cochrane Database Syst Rev. 2023 Jan 25;1(1):CD014962. doi: 10.1002/14651858.CD014962.pub2. Amstutz A et al. Lancet Respir Med. 2023 May;11(5):453-464. doi: 10.1016/S2213-2600(22)00528-8. Lee TC et al. Clin Microbiol Infect. 2022 Sep;28(9):1203-1210. doi: 10.1016/j.cmi.2022.04.018.
	Starker Konsens

Als Evidenzgrundlage zur Frühtherapie dient eine RCT mit insgesamt 562 ambulanten Patienten (27). Für ambulante Patienten (WHO Skala 2-3) mit Risikofaktoren für einen schweren Verlauf, die nicht geimpft waren und innerhalb von 7 Tagen nach Symptombeginn eine Therapie mit Remdesivir erhielten, zeigt sich eine signifikante Reduktion des kombinierten Endpunkts Krankenhausaufnahme oder Tod bis zum Tag 28 (ARR 4,6%; 95%KI 5,7% bis 1,6%; Qualität der Evidenz moderat). Für den Einsatz bei späteren Krankheitsstadien existieren teils heterogene Daten aus RCT und mehrere Meta-Analysen. Die Bewertung der Evidenz für Subgruppen nach Krankheitsschwere bzw. dem notwendigen respiratorischen Support wird durch uneinheitliche Differenzierung in RCT und Evidenzsynthesen, sowie teils überlappenden Studienpopulationen in Veröffentlichungen der WHO Solidarity Plattformstudie erschwert, welche nur durch Einbeziehung von Rohdaten teilweise überwunden werden können. In einer Cochrane Meta-Analyse von 2023 konnte unter Einbeziehung von neun RCTs mit 11,218 Patienten kein Mortalitätsvorteil festgestellt werden (28). Unter Verwendung von individuellen Patientendaten zeigte eine Meta-Analyse auf Grundlage von 8 Studien mit 10.751 hospitalisierten Patienten einen Mortalitätsvorteil für Patienten mit jeglicher Form der Sauerstofftherapie, welche keine invasive Beatmung benötigten und mit Remdesivir behandelt wurden gegenüber Placebo (RR 0.89 95%KI 0,79 bis 0,99) (29). Ein klinischer Nutzen für Patienten ohne Sauerstoffbedarf oder mit erforderlicher invasiver Beatmung konnte in dieser Arbeit nicht gezeigt werden. In einer weiteren Meta-Analyse wurden Patienten ohne Sauerstoffbedarf oder mit Low-Flow-Sauerstofftherapie gepoolt. Bei Patienten, welche mit Remdesivir behandelt wurden, ergab sich hierbei ebenfalls ein reduziertes Mortalitätsrisiko innerhalb von 28 Tagen im Vergleich zu Placebo (ARR 2%; 95% KI 0,7% bis 3,1%) (30). Ein Nutzen für Patienten mit High-Flow-Sauerstofftherapie bis hin zur invasiven Beatmung konnte nicht gezeigt werden. Aktuelle in vitro Daten lassen darauf schließen, dass Remdesivir auch bei den derzeit zirkulierenden Omikron Varianten effektiv ist (20, 31). Bisherige SARS-CoV-2-Varianten unterscheiden sich vor allem durch Mutationen im Bereich des viralen Spikeproteins und nicht in der RNA-Polymerase, welche das molekulare Ziel von Remdesivir ist. Die Verträglichkeit von Remdesivir war in allen Studien gut, wobei sich weniger SAE unter Remdesivir im Vergleich zu Placebo zeigten (Qualität der Evidenz niedrig) (28).

In Anbetracht der positiven Effekte auf das Risiko für Hospitalisierung oder Tod, welche im Rahmen der PINETREE Studie (27) verzeichnet wurden, spricht die Leitliniengruppe eine Empfehlung für den Einsatz in der Frühtherapie innerhalb von 7 Tagen nach Symptombeginn bei Personen mit einem hohem Risiko für einen schweren Verlauf aus. Auch wenn größere Studien an geimpften Patienten momentan fehlen, so geht die Leitliniengruppe, im Analogieschluss zu anderen antiviralen Substanzen, davon aus, dass auch bei geimpften Patienten mit Risikofaktoren für einen schweren Verlauf innerhalb der ersten 7 Tage nach Symptombeginn ein Benefit zu verzeichnen ist.

Aus der Meta-Analyse und den Ergebnissen der Einzelstudien kann keine Wirksamkeit für Patienten mit invasiver Beatmungsunterstützung abgeleitet werden. Die Aussagekraft von Subgruppenanalysen zur Krankheitsschwere ist aufgrund von methodischen Einschränkungen durch heterogene Studiendesigns limitiert. In der Zusammenschau insbesondere auch von Evidenzsynthesen, welche individuelle Patientendaten zur Verfügung hatten, lässt sich aber ein (geringer) Mortalitätsvorteil für Patienten mit Low-Flow-Sauerstofftherapie ableiten, daher wird eine offene Empfehlung für dieses Erkrankungsstadium abgegeben. Die Leitliniengruppe schließt sich damit auch der Bewertung des GBA an (32). Ein klinischer

Nutzen von Remdesivir für Patienten mit High-Flow-Sauerstofftherapie oder nicht-invasiver Beatmung (und damit regelhaft späterer Infektionsphase) ist nach Auffassung der Leitliniengruppe weiterhin unsicher.

Referenzen

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EMPFEHLUNG 3	**Evidenzbasierte Empfehlung, bestätigt 06/2024**
Empfehlungsgrad: **B ⇑**	**Bei Patienten mit persistierender (symptomatischer) SARS-CoV-2 Infektion und starker Immunsuppression (insbesondere anti-CD20, etc.) sollte eine antivirale Kombinationstherapie erfolgen.**
Qualität der Evidenz: **Frühphase** Viral Clearance: sehr niedrig ⊕⊖⊖⊖ Sterblichkeit: sehr niedrig ⊕⊖⊖⊖ Unerwünschte Ereignisse: sehr niedrig ⊕⊖⊖⊖	Literatur: Aiello TF et al. Influenza and Other Respiratory Viruses. 2024;18(3):e13264. DOI: https://doi.org/10.1111/irv.13264. Brosh-Nissimov T et al. J Microbiol Immunol Infect. 2024;57(1):189-194. DOI: 10.1016/j.jmii.2023.09.004. Gentile I et al. Virology Journal. 2023;20(1):301. DOI: 10.1186/s12985-023-02269-8. Huang L et al. International Journal of Infectious Diseases. 2024;141:106973. DOI: https://doi.org/10.1016/j.ijid.2024.02.016. Huygens S et al. Journal of Antimicrobial Chemotherapy. 2023;78(7):1644-1648. DOI: 10.1093/jac/dkad144 %J Journal of Antimicrobial Chemotherapy. Longo BM et al. Antibiotics (Basel). 2023;12(9):1460. Meijer SE et al. Journal of Infection and Chemotherapy. 2024;30(3):271-275. DOI: https://doi.org/10.1016/j.jiac.2023.10.022. Mikulska M et al. Clinical Infectious Diseases. 2023;77(2):280-286. DOI: 10.1093/cid/ciad181 %J Clinical Infectious Diseases. Pasquini Z et al. Hematological Oncology. 2023;41(5):904-911. DOI: https://doi.org/10.1002/hon.3206. Sanchez E et al. Transplant Infectious Disease. 2024;26(1):e14223. DOI: https://doi.org/10.1111/tid.14223. Upasani V et al. Clin Infect Dis. 2023;77(7):950-960. DOI: 10.1093/cid/ciad368.
	Starker Konsens

3.3.3. Immunmodulatorische Therapieansätze

3.3.3.1. Kortikosteroide

EMPFEHLUNG 4	Evidenzbasierte Empfehlung, bestätigt 12/2024
Empfehlungsgrad: A ⇑⇑	Bei Patienten mit durch COVID-19 Pneumonie-bedingter Sauerstofftherapie oder nicht-invasiver/invasiver Beatmung soll eine Therapie mit systemischen Kortikosteroiden erfolgen. Die Therapie sollte mit 6 mg Dexamethason p.o. oder i.v. über zehn Tage erfolgen.
Qualität der Evidenz:	Literatur: Horby P. et al. N Engl J Med. 2021 Feb 25;384(8):693-704. doi: 10.1056/NEJMoa2021436
30-Tage Sterblichkeit: moderat ⊕⊕⊕⊖ Unerwünschte Ereignisse: Sehr niedrig ⊕⊖⊖⊖	Tomazini BM et al. JAMA. 2020 Oct 6;324(13):1307-1316. doi: 10.1001/jama.2020.17021 Edalatifard M et al. Eur Respir J. 2020 Dec 24;56(6):2002808. doi: 10.1183/13993003.02808-2020 Dequin PF et al. JAMA. 2020 Oct 6;324(13):1298-1306. doi: 10.1001/jama.2020.16761 Jeronimo CMP et al. Clin Infect Dis. 2021 May 4;72(9):e373-e381. doi: 10.1093/cid/ciaa1177 Angus DC et al. JAMA. 2020 Oct 6;324(13):1317-1329. doi: 10.1001/jama.2020.17022 Wagner C, et al. Database Syst Rev 2022, Issue 11. Art. No.: CD014963. DOI: 10.1002/14651858.CD014963.pub2. Bouadma L. et al. JAMA Internal Medicine, 182(9), 906-916. doi: 10.1001/jamainternmed.2022.2168 Granholm A et al. Intensive care medicine, 48(5), 580-589. doi:10.1007/s00134-022-06677-2 Maskin LP, et al. J Intensive Care Med. 2022 Apr;37(4):491-499. doi: 10.1177/08850666211066799. Munch MW, et al.. JAMA 326(18): 1807-1817. doi: 10.1001/jama.2021.18295. Recovery Collaborative Group (2023). Lancet (london, england), 401(10387), 1499-1507. doi:10.1016/S0140-6736(23)00510-X Taboada M et al. Eur Respir J. 2022 Aug 4;60(2):2102518. doi: 10.1183/13993003.02518-2021. Toroghi N et al. Pharmacol Rep 2022 74(1): 229-240. doi: 10.1007/s43440-021-00341-0. Wu H et al. *PloS one, 17*(10), e0275217. doi:10.1371/journal.pone.0275217
	Starker Konsens

3.3.3.2. Tocilizumab (TCZ)

EMPFEHLUNG 5	Evidenzbasierte Empfehlung, bestätigt 12/2024
Empfehlungsgrad: 0 ↔	Tocilizumab kann bei COVID-19 Patienten mit progredient schwerer oder kritischer Erkrankung zur COVID-19-Behandlung in Kombination mit Steroiden (Dexamethason) verabreicht werden.

Qualität der Evidenz: 30 Tage Sterblichkeit: niedrig⊕⊕⊖⊖ Vermeidung der Zunahme der Krankheitsschwere (Progress zu notwendiger Invasiver Beatmung): niedrig⊕⊕⊖⊖ Schwere unerwünschte Ereignisse: sehr niedrig ⊕⊖⊖⊖ Unerwünschte Ereignisse: niedrig ⊕⊕⊖⊖	Literatur: RECOVERY Collaborative Group. Lancet. 2021 May 1;397(10285):1637-1645. doi: 10.1016/S0140-6736(21)00676-0 Gordon AC et al. N Engl J Med. 2021 Apr 22;384(16):1491-1502. doi: 10.1056/NEJMoa2100433 Rosas IO et al. N Engl J Med. 2021 Apr 22;384(16):1503-1516. doi: 10.1056/NEJMoa2028700 Salama C et al. The New England journal of medicine. 2021;384(1):20-30. doi:10.1056/NEJMoa2030340 Salvarani C et al. JAMA internal medicine. 2020. doi:10.1001/jamainternmed.2020.6615 Stone JH et al. The New England journal of medicine. 2020. doi:10.1056/NEJMoa2028836 Veiga VC et al. BMJ (Clinical research ed.). 2021;372:n84. doi:10.1136/bmj.n84 Soin AS et al. Lancet Respir Med. 2021;9(5):511-21. doi:10.1016/s2213-2600(21)00081-3 Hermine O et al. JAMA Intern Med. 2021;181(1):32-40. doi:10.1001/jamainternmed.2020.6820 Broman N et al. Clin Microbiol Infect. 2022;28(6):844-51. doi:10.1016/j.cmi.2022.02.027 Hermine O et al. EClinicalMedicine. 2022;46:101362. doi:10.1016/j.eclinm.2022.101362 Hermine O et al. Eur Respir J. 2022;60(2). doi:10.1183/13993003.02523-2021 Rosas IO et al. EClinicalMedicine. 2022;47:101409. doi:10.1016/j.eclinm.2022.101409 Wang D et al. Front Med. 2021;15(3):486-94. doi:10.1007/s11684-020-0824-3 Rutgers A et al. PLoS One. 2022;17(8):e0271807. doi:10.1371/journal.pone.0271807 Higgins AM et al. Jama. 2023;329(1):39-51. doi:10.1001/jama.2022.23257
	Starker Konsens

3.3.4. Nicht empfohlene Medikamente

EMPFEHLUNG 6	**Evidenzbasierte Empfehlung, bestätigt 12/2024**
Empfehlungsgrad: **A⇓⇓**	**Inhalative Steroide sollen nicht zur COVID-19-Therapie eingesetzt werden.**
Qualität der Evidenz: **Frühphase** 28-Tage-Sterblichkeit: sehr niedrig ⊕⊖⊖⊖ Hospitalisierung/Tod bis Tag 28: niedrig ⊕⊕⊖⊖	Literatur: Boulware DR et al. N Engl J Med. 2023;389(12):1085-95. doi:10.1056/NEJMoa2209421 Clemency BM et al. JAMA Intern Med. 2022;182(1):42-9. doi:10.1001/jamainternmed.2021.6759 Duvignaud A et al. Clin Microbiol Infect. 2022;28(7):1010-6. doi:10.1016/j.cmi.2022.02.031 Ezer N et al. Bmj. 2021;375:e068060. doi:10.1136/bmj-2021-068060
	Ramakrishnan S et al. Lancet Respir Med. 2021;9(7):763-72. doi:10.1016/s2213-2600(21)00160-0 Yu LM et al. Lancet. 2021;398(10303):843-55. doi:10.1016/s0140-6736(21)01744-x
	Starker Konsens

Monoklonale Antikörper

Virusneutralisierende monoklonale Antikörper (MAK) besitzen die Fähigkeit durch Interaktion mit dem SARS-CoV-2 Spikeprotein den Viruseintritt in die Zelle zu verhindern. Während der Pandemie wurden verschiedene monoklonale Antikörper (Bamlanivimab, Etesevimab Casirivimab/Imdevimab, Sotrovimab, Tixagevimab/Cilgavimab u. a.) zur Therapie von COVID-19 eingesetzt. In Anbetracht der positiven Effekte

auf das Risiko für Hospitalisierung oder Tod, welche im Rahmen der COMET-ICE Studie (107) vor dem Auftreten bzw. der Dominanz der Omikron-Variante verzeichnet wurden, sprach die Leitliniengruppe im Februar 2022 noch eine offene Empfehlung für den Einsatz von Sotrovimab in der Frühtherapie, bei nicht immunisierten Patienten innerhalb von 5 Tagen nach Symptombeginn, aus. **Gegen aktuell zirkulierende Omikron-Varianten (EG.5, BA. 286, JN.1) ist jedoch derzeit keiner der in Europa zur Therapie zugelassenen monoklonalen Antikörper klinisch ausreichend wirksam (17, 31, 108). Daher wird auch Sotrovimab für die Therapie von COVID-19 aktuell nicht mehr empfohlen.** Die US-amerikanische Arzneimittelbehörde FDA entzog dem monoklonalen Antikörper im April 2022 die Notfallzulassung. Eine Verdopplung der Sotrovimabdosis, die möglicherweise die Effektivität steigern würde, wurde von der Europäischen Arzneimittel-Agentur (EMA) mit Verweis auf fehlende Effektivitäts- und Sicherheitsdaten abgelehnt. Zuletzt wurden daher auch die Empfehlungen zur Prä-Expositionsprophylaxe mit Tixagevimab/Cilgavimab (Evusheld) weiter eingegrenzt. Eine Prä-Expositionsprophylaxe sollte nur noch in begründeten Einzelfällen in Betracht gezogen werden (17).

Referenzen

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National Institute for Health and Care Excellence (NICE), 2025 [5].

COVID-19 rapid guideline: managing COVID-19; NG191

Zielsetzung/Fragestellung

It provides guidance on managing COVID19. The guideline makes recommendations about care in all settings for adults, children and young people with clinically diagnosed or laboratory confirmed COVID-19.

Methodik

This guideline uses the methods and process in NICE's interim process and methods for guidelines developed in response to health and social care emergencies.

Grundlage der Leitlinie

- Repräsentatives Gremium: **trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**
- Systematische Suche, Auswahl und Bewertung der Evidenz: **trifft zu**
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: **trifft zu** (Prozess verkürzt)
- 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:

- Living guideline: Because there was a need for prompt guidance on managing COVID-19, NICE collaborated with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for this review. Evidence provided by the National Australian COVID-19 clinical

evidence taskforce was used through the sharing of RevMan files, which the NICE team used to populate the evidence summary section and GRADE profiles for this review.

- Letzte Aktualisierung: 01.05.2025

LoE/GoR

- GRADE

Sonstige methodische Hinweise

- Last updated May 2025: We amended the recommendation on nirmatrelvir plus ritonavir in line with NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19. See the technology appraisal's update information section for details.
- From March 2024, this guideline will be retired from living mode and will undergo surveillance and updates in line with Chapter 13.

Recommendations

4 Therapeutics for COVID-19

4.1 Antivirals

Nirmatrelvir and ritonavir

4.1.1 Nirmatrelvir plus ritonavir is recommended as an option for treating COVID-19 in adults, only if they:

- do not need supplemental oxygen for COVID-19 **and**
- have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

This recommendation is from NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab. [13 April 2022, amended 29 March 2023, 13 March 2024 and 1 May 2025]

Remdesivir

4.1.2 Remdesivir is recommended as an option for treating COVID-19 in hospitals in:

- adults, only if they have a high risk of serious illness (risk factors as defined in section 5 of NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19)
- babies, children and young people, only if they:
  - are aged 4 weeks to 17 years and weigh at least 3 kg, and:
    - have pneumonia, and
    - need supplemental oxygen, or
  - weigh at least 40 kg, and have a high risk of serious illness (risk factors as defined in section 5 of NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab for treating COVID-19).

Remdesivir is only recommended if the company provides it according to the commercial arrangement (see section 2 of NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab for treating COVID-19).

This recommendation is from NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab. [**23 March 2021, amended 29 March 2023 and 8 May 2024]**

Molnupiravir

4.1.3 Consider a 5-day course of molnupiravir for adults with COVID-19 who:

- do not need supplemental oxygen for COVID-19 **and**
- are within 5 days of symptom onset **and**
- are thought to be at high risk of progression to severe COVID-19. (NHS England's Interim Clinical Commissioning Policy on remdesivir and molnupiravir provides a list of people prioritised for treatment with antivirals.)

When assessing the person, take into account their likely response to any vaccinations already given, any comorbidities or risk factors, and whether their condition is deteriorating. **[23 March 2021, amended 29 March 2023]**

4.1.4 Do not offer molnupiravir to children and young people aged under 18, or pregnant women. **[23 March 2021, amended 29 March 2023]**

4.2 Sotrovimab

4.2.1 Sotrovimab is recommended as an option for treating COVID-19 in adults and young people aged 12 years and over and weighing at least 40 kg, only if:

- they do not need supplemental oxygen for COVID-19 **and**
- they have an increased risk for progression to severe COVID-19, as defined in section 5 of NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab **and**
- nirmatrelvir plus ritonavir is contraindicated or unsuitable.

Sotrovimab is only recommended if the company provides it according to the commercial arrangement.

This recommendation is from NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab. **[27 January 2022, amended 29 March 2023 and 13 March 2024]**

4.3 Corticosteroids

4.3.1 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. **[8 April 2021]**

4.3.2 Do not use corticosteroids to treat COVID-19 in people who do not need supplemental oxygen. (People who need corticosteroids for another medical reason should still have them.) **[8 April 2021, amended 20 April 2022]**

4.4 Casirivimab and imdevimab – for people hospitalised because of COVID-19

4.4.1 This recommendation has been deleted because the conditional marketing authorisation for casirivimab plus imdevimab for treating COVID-19 was withdrawn. **[13 March 2024]**

4.5 Tocilizumab

4.5.1 Tocilizumab is recommended, within its marketing authorisation, as an option for treating COVID-19 in adults who:

- are having systemic corticosteroids **and**
- need supplemental oxygen or mechanical ventilation.

Tocilizumab is only recommended if the company provides it according to the commercial arrangement.

This recommendation is from NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

The summary of product characteristics for tocilizumab specifies that it should only be offered when there is no evidence of a bacterial or viral infection (other than SARS-CoV-2) that might be worsened by tocilizumab. It also states that the efficacy of tocilizumab has not been established in the treatment of COVID-19 in people who do not have elevated C-reactive protein levels. **[8 April 2021, amended 29 March 2023 and 13 March 2024]**

4.6 Baricitinib

4.6.1 Consider baricitinib for people 2 years and over in hospital with COVID-19 who:

- need supplemental oxygen for COVID-19 **and**
- are having or have completed a course of corticosteroids such as dexamethasone, unless they cannot have corticosteroids **and**
- have no evidence of infection (other than SARS-CoV-2) that might be worsened by baricitinib.

In March 2023, this was an off-label use of baricitinib. See NICE's information on prescribing medicines. Baricitinib may be considered in people who meet the above criteria, and who cannot have tocilizumab. When there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to add baricitinib.

Baricitinib is contraindicated in pregnancy and breastfeeding. The Royal College of Obstetricians and Gynaecologists has produced guidance on managing coronavirus infection in pregnancy**. [6 May 2022, amended 29 March 2023]**

4.7 Antibiotics

4.7.1 Do not use antibiotics 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. **[21 March 2021, amended 3 June 2021]**

4.8 Azithromycin

4.8.1 Do not use azithromycin to treat COVID-19. **[3 June 2021]**

4.9 Budesonide (inhaled)

4.9.1 Only use budesonide to treat COVID-19 as part of a clinical trial. (People already on budesonide for conditions other than COVID-19 should continue treatment if they test positive for COVID-19.) **[3 November 2021]**

4.10 Colchicine

4.10.1 Do not use colchicine to treat COVID-19. **[27 May 2021, amended 1 December 2021]**

4.11 Doxycycline

4.11.1 Do not use doxycycline to treat COVID-19 in the community. **[2 September 2021]**

4.12 Ivermectin

4.12.1 Do not use ivermectin to treat COVID-19 except as part of an ongoing clinical

trial. **[22 November 2021, amended 15 June 2022]**

4.13 Tixagevimab plus cilgavimab

4.13.1 Tixagevimab plus cilgavimab is not recommended, within its marketing authorisation, for treating COVID-19 in adults who do not need supplemental oxygen and who have an increased risk of progression to severe COVID-19.

This recommendation is from NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab for treating COVID-19. **[8 May 2024]**

4.14 Vitamin D

4.14.1 Do not use vitamin D to treat COVID-19 except as part of a clinical trial.

For existing UK guidance on taking vitamin D to maintain muscle and bone health, see NHS advice on vitamin D. **[14 July 2022]**

Rationales

Antivirals

Nirmatrelvir and ritonavir

Recommendation 4.1.1

Clinical evidence suggests that nirmatrelvir plus ritonavir is effective at treating mild COVID-19 compared with standard care. Nirmatrelvir plus ritonavir is recommended in these groups because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. For evidence and information on how this decision was made, see NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Remdesivir

Recommendation 4.1.2

For adults in hospital, remdesivir can improve how long adults needing low-flow supplemental oxygen live compared with standard care, but the evidence is highly uncertain. The cost-effectiveness estimates for remdesivir are only likely to be within what NICE considers an acceptable use of NHS resources for adults in hospital who have a high risk of serious illness. So, remdesivir is recommended for treating COVID-19 in this group.

There is limited clinical evidence comparing remdesivir with standard care for treating severe COVID-19 in babies, children and young people. So, the cost-effectiveness estimates are highly uncertain. But there are limited treatment options licensed for the groups covered, and the number who would have remdesivir is very small. So, remdesivir is recommended for treating COVID-19 in these groups.

Molnupiravir

Recommendation 4.1.3

There is evidence from 2 randomised controlled trials that treatment with molnupiravir within 5 days of symptom onset reduces the risk of hospitalisation or death compared with placebo in adults who do not need supplemental oxygen and have at least 1 risk factor for development of severe COVID-19 disease. However, there is uncertainty about the generalisability of the evidence to current clinical practice because the trials only included people who were not vaccinated against COVID-19, and took place before the emergence of the Omicron (B.1.1.529) variant. Clinicians should refer to the NHS England Interim Clinical Commissioning Policy for the most up-to-date information about people prioritised for treatment with antivirals.

Recommendation 4.1.4

Two trials were included in the evidence, and both trials only included people aged 18 and above. Pregnant women were also excluded from the study population.

The summary of product characteristics states that molnupiravir is of low risk for mutagenicity or genotoxicity in adults. However, the safety and efficacy of molnupiravir has not been established in children and young people or pregnant women. Based on this, and the absence of these groups from the study populations, the panel concluded that there is no evidence on the efficacy and safety of molnupiravir for children and young people, or pregnant women, and so it cannot be recommended for them.

Sotrovimab

Recommendation 4.2.1

There is some evidence suggesting that sotrovimab is likely to be effective at treating mild COVID-19 compared with standard care. Its likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources for people in whom nirmatrelvir plus ritonavir is contraindicated or unsuitable. So, sotrovimab is recommended for this group.

Corticosteroids

Recommendation 4.3.1

There is evidence to support using corticosteroids for people with COVID-19 who need supplemental oxygen, or who have a level of hypoxia that needs supplemental oxygen but

who are unable to have or tolerate it. It is now established standard practice to offer dexamethasone. The growing evidence base, combined with its widespread availability, ease of administration and acceptable safety profile, supports its continued use. Hydrocortisone and prednisolone are suitable alternatives if dexamethasone cannot be used or is unavailable. The course duration recommended, for up to 10 days unless there is a clear indication to stop early, is based on that used in clinical trials. This includes being discharged 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.)

Recommendation 4.3.2

Evidence suggests that, in people with COVID-19 who do not need supplemental oxygen, corticosteroids may increase the risk of needing invasive mechanical ventilation and death at 28 days. The recommendation therefore cautions against using corticosteroids for people not on supplemental oxygen, unless there is another medical indication to do so.

Tocilizumab

Recommendation 4.5.1

Clinical evidence suggests that tocilizumab is effective at treating severe COVID-19 compared with standard care. Tocilizumab is recommended because the likely cost-effectiveness estimates are within what NICE considers an acceptable use of NHS resources. For evidence and information on how this decision was made, see NICE's technology appraisal guidance on nirmatrelvir plus ritonavir, sotrovimab and tocilizumab.

Baricitinib

Recommendation 4.6.1

There is evidence to support the use of baricitinib for moderate to severe COVID-19 in adults in hospital. It shows that baricitinib reduces mortality, duration of hospital stay and disease severity. Corticosteroids are part of standard treatment for COVID-19 in the UK, and there is evidence of an additional benefit when baricitinib is also used.

Baricitinib is not licensed for treating COVID-19. Off-label use of baricitinib for COVID-19 may be an option for adults who cannot have tocilizumab (for example, when tocilizumab is not available, the person cannot tolerate intravenous administration, or there are other important patient preferences or circumstances). The panel noted that, when there is clinical deterioration despite treatment with tocilizumab, it may be appropriate to also add baricitinib.

Based on the evidence supporting the use of baricitinib for moderate to severe COVID-19 in adults, the panel agreed that, in the event of severe or deteriorating illness, it could also be considered for children and young people 2 years and over. This is after careful clinical risk assessment and shared decision making that includes expert input from paediatricians and paediatric infectious disease specialists.

Azithromycin

Recommendation 4.8.1

The evidence suggests that azithromycin is no better than standard care at reducing risk of death in people in hospital with COVID-19. Limited evidence also suggests that azithromycin does not reduce the risk of hospitalisation or death in people with COVID-19 in the community. There is no evidence for azithromycin use for COVID-19 in children. The panel did not think there were reasons to expect different results in this group, so agreed

that the recommendation applies to all age groups. They also noted the risk of antimicrobial resistance with azithromycin.

Budesonide (inhaled)

Recommendation 4.9.1

Trial evidence suggests some benefit with inhaled budesonide in reducing how long it takes to recover from COVID-19. However, this evidence is limited because it comes from only 2 trials, 1 of which was very small and stopped early. Also, the population in the trials was mainly older people, which limits its generalisability to other age groups. The panel concluded that more research is needed to address these issues, and that inhaled budesonide should therefore only be used as part of a clinical trial. They also made a recommendation for research to address this.

Colchicine

Recommendation 4.10.1

The evidence from trials of colchicine to treat COVID-19 in adults, both in hospital and community settings, shows no beneficial effect on all-cause mortality or need for mechanical ventilation compared with standard care. It also shows no effect on duration of hospital stay or hospitalisation. The evidence also shows that colchicine causes statistically significantly more adverse events than standard care within 21 days of starting treatment in hospital or 30 days in the community. There is no evidence for children or young people. Therefore, colchicine should not be used to treat COVID-19 in people of any age.

Doxycycline

Recommendation 4.11.1

There is evidence from 1 trial in the community of doxycycline for COVID-19 in people 65 years and over and in people 50 years and over with comorbidities. The results suggest that, compared with standard care alone, doxycycline plus standard care does not reduce the risk of hospitalisation and death, admission to intensive care, the need for mechanical ventilation or oxygen, or significant adverse events in these groups. The results also suggest that it does not improve symptoms or recovery.

There is no evidence for doxycycline use in the community for COVID-19 in people under 65 years or people under 50 years with comorbidities. But, it is unlikely that the results in these groups will differ, so the panel agreed that the recommendation applies to all age groups in the community. They also noted the risks of side effects and antimicrobial resistance with doxycycline. There was no evidence found for doxycycline use in hospital settings.

Ivermectin

Recommendation 4.12.1

Overall, there is a high degree of uncertainty about whether ivermectin is more effective than control (standard care, placebo or both) for managing COVID-19 in hospital or community settings. The panel raised concerns about the quality of the studies on ivermectin. They noted that most of the evidence is of low or very low certainty, with some that is of moderate certainty. The panel also noted the uncertainty about the overall safety and the possibility of rare serious adverse reactions with ivermectin. Because of the uncertainty in the evidence (including small sample sizes and issues with study quality), the

panel agreed that ivermectin should only be used to treat COVID-19 in ongoing well-conducted clinical trials. The panel were aware of at least 1 ongoing trial, the results of which may improve the certainty of the evidence on the effectiveness of ivermectin for managing COVID-19.

Tixagevimab plus cilgavimab

Recommendation 4.13.1

Evidence suggests that it is highly uncertain that tixagevimab plus cilgavimab is effective against Omicron variants of COVID-19. Because of this, it is not possible to reliably estimate its cost effectiveness, so it is not recommended. For evidence and information on how this decision was made, see NICE's technology appraisal guidance on remdesivir and tixagevimab plus cilgavimab.

Vitamin D

Recommendation 4.14.1

The panel agreed that the clinical-effectiveness evidence for vitamin D for treating COVID-19 is uncertain, but suggests that there is no clear evidence of benefit. The studies included diverse populations with different COVID-19 severity, and used varying dosages of vitamin D and definitions of standard care. This means the evidence may not be generalisable to the UK.

The panel noted that the daily doses used in the studies were far higher than the standard doses used to prevent or treat vitamin D deficiency in the UK. They also noted that there was limited evidence from the studies on the adverse effects of these doses of vitamin D. The panel pointed out the potential adverse effects of a vitamin D overdose, such as raised plasma and urine concentrations of calcium and phosphate, and nausea and vomiting (see the BNF for more details on adverse effects).

The panel highlighted that existing guidance recommends taking vitamin D to maintain muscle and bone health. They agreed that vitamin D is important and well established for this.

The panel agreed that, until there is more evidence on the effects of vitamin D for treating COVID-19, it should only be used for treating COVID-19 as part of a clinical trial. The panel noted that the study populations did not include pregnant women or older populations who may be at more risk of severe COVID-19 outcomes. They also did not include children and young people under 18 years. So, they agreed that more research is also needed in the area and made a recommendation for research on vitamin D for treating COVID-19.

Bhimraj A et al., 2024 [3].

Infectious Diseases Society of America (IDSA)

IDSA Guidelines on the Treatment and Management of Patients with COVID-19

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

Published by IDSA, 5/27/2021

- Repräsentatives Gremium: **trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**
- 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**

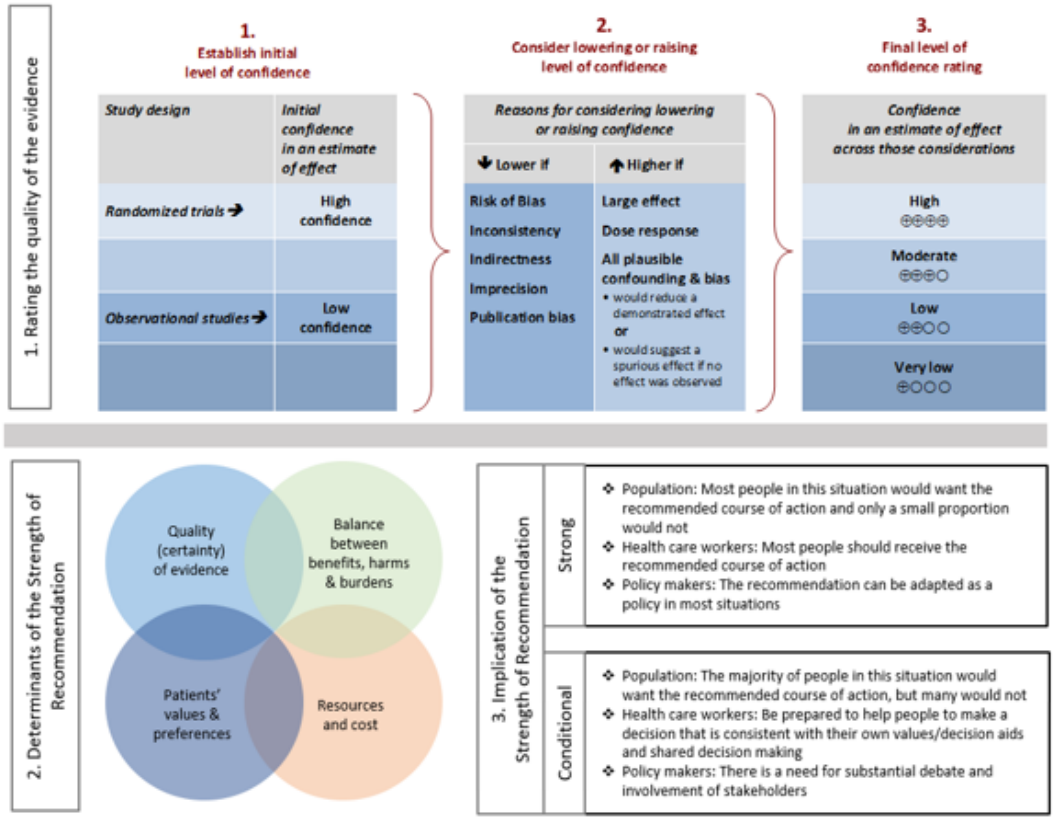
Recherche/Suchzeitraum:

- Per living guideline approach, monthly searches are conducted in Ovid Medline and Embase, building on the literature searched from 2019. This document reflect literature searched through May 31, 2022
- Horizon scans have been performed regularly during the evidence assessment and recommendation process to locate additional grey literature, including manuscript pre-prints
- Letzte Aktualisierung: 8/12/2024

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 or harmful interventions.

Figure 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)



<u>Sonstige methodische Hinweise</u>

- This guideline was developed in two stages. First, an initial rapid systematic review was conducted to inform the first iteration of the guideline. Second, while maintaining a current evidence based, the guideline scope expanded to update existing recommendations and include additional therapies, as needed, using a living guideline approach. Given the need for continued urgent responses to this major public health crisis, the methodological approach follows the Guidelines International Network/McMaster checklist for the development of rapid recommendations.
- Changes to these guidelines falls into one of three categories: update, amendment, or retirement. An update involves a search for new studies, and if any new studies are found, they will be critically appraised and the pertinent section will be removed and replaced with the updated section. An amendment involves a change or correction to the document without any search for new studies and their appraisal. It will also involve changes made to clarify or explain a section based on "living" feedback from the readers. Due to lack of continued relevancy of a treatment option, the guideline panel may choose to retire a section. While the retired section will not appear in the manuscript, all sections with accompanying dates will be available on the IDSA website.

Executive Summary

Neutralizing Antibodies for Pre-Exposure Prophylaxis (Pemivibart)

Recommendation:

In moderately or severely immunocompromised individuals 12 years or older at risk for progression to severe COVID-19, the IDSA guideline panel suggests pre-exposure prophylaxis with pemivibart when predominant regional variants are susceptible to the agent (conditional recommendation, low certainty of evidence).

- The anticipated benefit is likely greatest in people who are the most immunocompromised because they have the highest risk of inadequate immune response and progression to severe disease.
- The anticipated benefit may be lower in patients aged 12 to 17 years, who have less severe COVID-19 outcomes than adults, as reflected by lower rates of hospitalization.
- As the evidence is based on immunobridging and circulating variant susceptibility is evolving, additional clinical and laboratory data may impact this recommendation.
- Patients who place a higher value on potential harms, specifically, the observed 0.6% risk of anaphylaxis, and a lower value on the uncertain benefits of prevention of severe COVID-19 would reasonably decline pemivibart.
- Per the FDA EUA, pemivibart is authorized to be given at 4,500 mg IV every 3 months.
- Per the FDA EUA, in individuals who have recently received a COVID-19 vaccine, pemivibart should be administered at least 2 weeks after vaccination.

*Conditional recommendations are made when the suggested course of action would apply to the majority of people with many exceptions, and shared decision-making is important.

EVUSHELD (Archived)

Hinweis: Section last reviewed and updated on 1/27/2023.

As of 1/26/2023, based on CDC Nowcast data, fewer than 10% of circulating variants in the US are susceptible to tixagevimab/cilgavimab (Evusheld), the sole product that has been available for pre-exposure prophylaxis. Tixagevimab/cilgavimab is therefore no longer authorized for use in the US until further notice by FDA.

Neutralizing Antibodies for Post-Exposure Prophylaxis (Archived)

Hinweis: Section last reviewed and updated on 1/12/2023.

The first two US FDA authorized anti-SARS-CoV-2 neutralizing antibody combinations, bamlanivimab/etesevimab and casirivimab/imdevimab, were found to be largely inactive against the Omicron BA.1 and BA.2 variants, rendering these products no longer useful for either treatment or post-exposure prophylaxis. As a result, Emergency Use Authorization was withdrawn by the US FDA for both bamlanivimab/etesevimab and casirivimab/imdevimab, leaving no available neutralizing antibody product for use in the United States for post-exposure prophylaxis.

Vilobelimab

This recommendation is endorsed by the Society of Critical Care Medicine (SCCM), the Society for Healthcare Epidemiology of America (SHEA), and the Society of Infectious Diseases Pharmacists (SIDP)

Section last reviewed on 02/12/2025

Last literature search conducted 11/01/2024

Recommendation 1:

In hospitalized adults with critical COVID-19 requiring mechanical ventilation or ECMO, the IDSA guideline panel recommends vilobelimab only in the context of a clinical trial **(knowledge gap)**

- Remark: Critical illness is defined as patients on mechanical ventilation and/or ECMO.

Hydroxychloroquine/Chloroquine + Azithromycin

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 12/23/2020

Last literature search conducted 12/14/2020

Recommendation 1:

Among 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 for Prophylaxis

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 9/23/2021

Last literature search conducted 9/21/2021

Recommendation 3:

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

Lopinavir/Ritonavir

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 2/16/2022

Last literature search conducted 1/31/2022

Recommendation 4:

In persons exposed to COVID-19, the IDSA guideline panel recommends against post-exposure prophylaxis with lopinavir/ritonavir. (**Strong recommendation, Moderate certainty of evidence**)

Recommendation 5:

Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel recommends against the use of lopinavir/ritonavir. (**Strong recommendation, Moderate certainty of evidence**)

Recommendation 6:

Among hospitalized patients with COVID-19, the IDSA guideline panel recommends against the use of the combination lopinavir/ritonavir. (**Strong recommendation, Moderate certainty of evidence**)

Glucocorticoids

Section last reviewed and updated 9/25/2020

Last literature search conducted 9/4/2020

Recommendation 7:

Among hospitalized critically ill patients* with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone. (**Strong recommendation, Moderate certainty of evidence**)

- Remark: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone is unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 8:

Among hospitalized patients with severe**, but non-critical, COVID-19, the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. **(Conditional recommendation†, Moderate certainty of evidence**)

- Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone is unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.

Recommendation 9:

Among hospitalized patients with mild-to-moderate*** 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 extracorporeal mechanical oxygenation (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 SpO2 ≤94% on room air, including patients on supplemental oxygen.

***Mild-to-moderate illness is defined as patient with a SpO2 >94% not requiring supplemental oxygen.

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Inhaled Corticosteroids

Recommendation 10:

Among ambulatory patients with mild-to-moderate COVID-19, the IDSA guideline panel suggests against inhaled corticosteroids. **(Conditional recommendation††, Moderate certainty of evidence**)

- Remark: Patients who are on inhaled corticosteroids for other indications may continue them.

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Interleukin-6 Inhibitors (Tocilizumab and Sarilumab)

Section last reviewed and updated on 9/14/2021

Last literature search conducted 8/31/2021

Recommendation 11:

Among hospitalized adults with progressive severe* or critical** COVID-19 who have elevated markers of systemic inflammation, the IDSA guideline panel suggests tocilizumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (**Conditional recommendation†, Low certainty of evidence**)

- 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 12:

When tocilizumab is not available, for patients who would otherwise qualify for tocilizumab, the IDSA guideline panel suggests sarilumab in addition to standard of care (i.e., steroids) rather than standard of care alone. (**Conditional recommendation†, Very low certainty of evidence**)

- Remark: Patients, particularly those who respond to steroids alone, who put a high value on avoiding possible adverse events of sarilumab and a low value on the uncertain mortality reduction, would reasonably decline sarilumab.

Severity definitions:

*Severe illness is defined as patients with SpO2 ≤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.

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Convalescent Plasma

Section last reviewed and updated on 2/22/2023

Last literature search conducted 1/31/2023

Recommendation 13(UPDATED 2/22/2023):

Among immunocompetent patients hospitalized with COVID-19, the IDSA guideline panel recommends against COVID-19 convalescent plasma. (**Strong recommendation, Moderate certainty of evidence).**

Recommendation 14(NEW 2/22/2023):

Among immunocompromised patients hospitalized with COVID-19, the IDSA guideline panel suggests against the routine use of COVID-19 convalescent plasma. (**Conditional recommendation, very low certainty of evidence).**

- Remark: Patients, particularly those who do not qualify for other treatments, who place a higher value on the uncertain mortality reduction and a lower value on the potential adverse effects of convalescent plasma would reasonably select convalescent plasma.

Recommendation 15(UPDATED 2/22/2023):

Among ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests FDA-qualified high-titer COVID-19 convalescent plasma within 8 days of symptom onset rather than no high-titer COVID-19 convalescent plasma. **(Conditional recommendation†, Low certainty of evidence)**

Remarks:

- In the United States, FDA emergency use authorization (EUA) only authorizes use in patients with immunosuppressive disease or receiving immunosuppressive treatment.
- Patients, particularly those who are not immunocompromised, who place a low value on the uncertain benefits (reduction in the need for mechanical ventilation, hospitalization, and death) and a high value on avoiding possible adverse events associated with convalescent plasma would reasonably decline convalescent plasma.
- Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir and three-day treatment with remdesivir Patient-specific factors (e.g., symptom duration, renal insufficiency or other contraindications, drug interactions) as well as logistical challenges, infusion capacity, and product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Remdesivir

Section last reviewed and updated 2/7/2022

Last literature search conducted 1/31/2022

Recommendation 16:

Among patients (ambulatory or hospitalized) with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests remdesivir initiated within seven days of symptom onset rather than no remdesivir. **(Conditional recommendation†, Low certainty of evidence)**

- Remarks:
  - Dosing for remdesivir in mild-to-moderate COVID-19 is 200 mg on day one followed by 100 mg on days two and three. Pediatric dosing is 5 mg/kg on day 1 and 2.5 mg/kg on subsequent days.

- Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, molnupiravir, and neutralizing monoclonal antibodies. Patient-specific factors (e.g., patient age, symptom duration, renal function, drug interactions), product availability, and institutional capacity and infrastructure should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

Recommendation 17:

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 18a:

In hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment. (**Conditional recommendation†, Moderate certainty of evidence**)

Recommendation 18b:

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**)

Severity definition:

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

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a

Famotidine

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 5/23/2022

Last literature search conducted 4/30/2022

Recommendation 19:

Among ambulatory patients with mild-to-moderate COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19 **(Conditional recommendation††, Low certainty of evidence).**

Recommendation 20:

Among hospitalized patients with severe* COVID-19, the IDSA panel suggests against famotidine for the treatment of COVID-19. **(Conditional recommendation††, Low certainty of evidence)**

Severity definition:

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

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Neutralizing Antibodies for Treatment

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 1/12/2023

- During 2022, multiple Omicron sub-variants with progressively greater in vitro reductions in susceptibility to multiple anti-SARS CoV-2 neutralizing antibodies emerged. On November 30, 2022, the US FDA withdrew Emergency Use Authorization for bebtelovimab, the one anti-SARS CoV-2 neutralizing antibody product that had retained in vitro activity against most previously circulating SARS-CoV-2 variants, leaving no available neutralizing antibody product in the United States for treatment of COVID-19.

Janus Kinase Inhibitors (Baricitinib and Tofacitinib)

Baricitinib

Section last reviewed and updated 4/29/2022

Last literature search conducted 3/31/2022

Recommendation 21:

Among hospitalized adults with severe* COVID-19, the IDSA panel suggests baricitinib with corticosteroids 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.

Recommendation 22:

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.

Tofacitinib

Section last reviewed and updated 8/21/2021

Last literature search conducted 7/31/2021

Recommendation 23:

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.

Severity definitions:

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

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

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Ivermectin

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 10/10/2022

Last literature search conducted 8/31/2022

Recommendation 24:

In hospitalized patients with COVID-19, the IDSA panel suggests against ivermectin. **(Conditional recommendation††, Very low certainty of evidence)**

Recommendation 25:

In ambulatory persons with COVID-19, the IDSA panel recommends against ivermectin. **(Strong recommendation, Moderate certainty of evidence)**

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Fluvoxamine

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 11/8/2021

Last literature search conducted 10/31/2021

Recommendation 26:

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

Nirmatrelvir/Ritonavir

Section last reviewed and updated 4/12/2023

Last literature search conducted 3/31/2023

Recommendation 27(UPDATED 4/12/2023):

In ambulatory patients with mild-to-moderate COVID-19 at high risk for progression to severe disease, the IDSA guideline panel suggests nirmatrelvir/ritonavir initiated within five days of symptom onset rather than no nirmatrelvir/ritonavir. **(Conditional recommendation†, Low certainty of evidence)**

- Remarks:

- Patients' medications need to be screened for serious drug interactions
- Dosing based on renal function:
- Estimated glomerular filtration rate (eGFR) > 60 ml/min: 300 mg nirmatrelvir/100 ritonavir every 12 hours for five days
- eGFR ≤60 mL/min and ≥30 mL/min: 150 mg nirmatrelvir/100 mg ritonavir every 12 hours for five days
- eGFR <30 mL/min: not recommended
- Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital may also receive nirmatrelvir/ritonavir

Options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, remdesivir for a 3-day course, molnupiravir, and neutralizing monoclonal antibodies. Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Molnupiravir

Section last reviewed and updated 2/23/2023

Last literature search conducted 1/31/2023

Recommendation 28:

In ambulatory patients (≥18 years) with mild-to-moderate COVID-19 at high risk for progression to severe disease who have no other treatment options*, the IDSA guideline panel suggests molnupiravir initiated within five days of symptom onset rather than no molnupiravir. (**Conditional recommendation†, Low certainty of evidence**)

*Other options for treatment and management of ambulatory patients include nirmatrelvir/ritonavir, three-day treatment with remdesivir, Patient-specific factors (e.g., symptom duration, renal function, drug interactions) as well as product availability should drive decision-making regarding choice of agent. Data for combination treatment do not exist in this setting.

- Remarks:
  - Patients who will most likely benefit from antivirals are those with risk factors for progression to severe disease (e.g., elderly, those with high-risk comorbidities, incomplete vaccination status, or immunocompromised). Those without risk factors are less likely to benefit.
  - Patients who put a higher value on the putative mutagenesis, adverse events, or reproductive concerns and a lower value on the uncertain benefits would reasonably decline molnupiravir.
  - Patients with mild-to-moderate COVID-19 who are at high risk of progression to severe disease admitted to the hospital for reasons other than COVID-19 may also receive molnupiravir.
  - Molnupiravir is not authorized under the FDA EUA for use in patients <18 years because it may affect bone and cartilage growth.
  - Molnupiravir is not recommended under the FDA EUA for use during pregnancy.
  - Molnupiravir is not authorized under the FDA EUA for pre-exposure or post-exposure prevention of COVID-19 or for initiation of treatment in patients hospitalized due to COVID-19 because benefit of treatment has not been observed in individuals when treatment is started after hospitalization due to COVID-19.

†The guideline panel concluded that the desirable effects outweigh the undesirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Colchicine

Note: There will be no continuous literature search or review for recommendation(s) within this section.

Section last reviewed and updated 6/30/2022

Last literature search conducted 5/31/2022

Recommendation 29:

In hospitalized patients with COVID-19, the IDSA panel recommends against colchicine for treatment of COVID-19. (**Strong recommendation, Moderate certainty of evidence**)

Recommendation 30:

In ambulatory persons with COVID-19, the IDSA panel suggests against colchicine for treatment of COVID-19. (**Conditional recommendation††, Moderate certainty of evidence**)

††The guideline panel concluded that the undesirable effects outweigh the desirable effects, though uncertainty still exists, and most informed people would choose the suggested course of action, while a substantial number would not.

Anakinra

Section last reviewed and updated 5/4/2023

Last literature search conducted 3/31/2023

Recommendation 31(NEW 5/4/2023):

In hospitalized patients with severe* COVID-19, the IDSA guideline panel suggests against the routine use of anakinra. **(Conditional recommendation, Low certainty of evidence**)

Severity definitions:

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

Acute SARS-CoV-2 Infection in Children

Management

Remdesivir

The studies involving the use of remdesivir in hospitalized patients with COVID-19 (recommendations 15-17) [32, 159-161, 313] have generally focused on individuals over age 18 years. Two trials included children over 12 years [161, 313], but did not separately report the number or outcomes (including adverse events) of participants under 18 years. Nevertheless, remdesivir is commonly used and recommended by expert panels [314] of pediatric ID specialists in hospitalized children with SARS-CoV-2 infection, and reports suggest low adverse event rates [162, 315]. An ongoing phase II/III open label study in children (the "CARAVAN" trial) [163] has not yet reported their results in the peer-reviewed literature [316]. Recent studies of outpatient remdesivir treatment in individuals at high risk for progression support its use in pediatric patients down to 3.5 kg of body weight.

Referenzen:

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315.Gotzinger F, Santiago-Garcia B, Noguera-Julian A, et al. COVID-19 in children and adolescents in Europe: a multinational, multicentre cohort study. Lancet Child Adolesc Health 2020; 4(9): 653-61.

Corticosteroids

Dexamethasone and other corticosteroids are recommended in certain hospitalized patients with COVID-19 (recommendations 7-9). The studies informing these recommendations [79, 95] either did not include children or did not separately report the number or outcomes (including adverse events) of participants under 18 [95] years. Corticosteroid use is nevertheless common in hospitalized children with COVID-19 [311], and there is reason to believe that the risk benefit ratio would be similar in children and adults.

IL-6 blockade

Tocilizumab or sarilumab is suggested for use in treatment of COVID-19 in certain situations (recommendations 11-12). Of the studies informing the recommendations for tocilizumab [110, 111, 113-116, 317, 318], only two [110, 111] did not specifically exclude children under 18 years from enrolling. The RECOVERY trial included children, but results from those in the tocilizumab arm of the trial have not yet been reported. Hermine et al. did not specifically exclude children, but results in children were not separately reported either.

Three of the four studies used to inform the recommendations for sarilumab excluded children from participation [117, 118, 317]. The pre-print network meta-analysis of 18 RCTs of IL-6 inhibitors included some studies that enrolled children, but results in children were not separately reported.

There are several publications reporting on cohorts of children with COVID-19 who received treatment with tocilizumab [315, 319-321]. Although there have been no clear contraindications to using IL-6 inhibitors in children based on these reports more studies in children are needed to determine whether the criteria for their pediatric use would be similar to those in adults.

JAK inhibitors

Baricitinib is suggested for use in treating certain hospitalized patients with COVID-19 (recommendations 21-22). However, the studies which inform these recommendations did not include children [176, 181, 182, 278]. Although the EUA for use of baricitinib in treatment of COVID-19 extends to children over 2 years of age [322], baricitinib does not have an FDA indication for treatment of other conditions in children, and there are only limited published pediatric pharmacokinetic data [323]. A pediatric safety and pharmacokinetic study on baricitinib use in children with COVID-19 is now recruiting [324].

Tofacitinib is also suggested for use in treating certain hospitalized patients with COVID-19 (recommendation 23). As with baricitinib, the trial informing this recommendation did not include children [185]. Tofacitinib is used in children over age 2 and over 10 kg for treatment of polyarticular juvenile idiopathic arthritis when they have had an inadequate response or intolerance to one or more tumor necrosis factor inhibitors [325]. There are no currently open trials studying tofacitinib for treatment of COVID-19 in children.

Referenzen:
176. Marconi VC, Ramanan AV, de Bono S, et al. Baricitinib plus Standard of Care for Hospitalized Adults with COVID-19. medRxiv 2021: Available at: https://doi.org/10.1101/2021.04.30.21255934 [Preprint 3 May 2021].
181. Kalil AC, Patterson TF, Mehta AK, et al. Baricitinib plus Remdesivir for Hospitalized Adults with Covid-19. N Engl J Med 2021; 384: 795-807.
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278. Ely EW, Ramanan AV, Kartman CE, et al. Baricitinib plus Standard of Care for Hospitalised Adults with COVID-19 on Invasive Mechanical Ventilation or Extracorporeal Membrane Oxygenation: Results of a Randomised, Placebo-Controlled Trial. medRxiv 2021: Available at: https://doi.org/10.1101/2021.10.11.21263897 [Preprint 12 October 2021].
323.Kim H, Brooks KM, Tang CC, et al. Pharmacokinetics, Pharmacodynamics, and Proposed Dosing of the Oral JAK1 and JAK2 Inhibitor Baricitinib in Pediatric and Young Adult CANDLE and SAVI Patients. Clin Pharmacol Ther 2018; 104(2): 364-73.
324. Eli Lilly and Company. A Study of Baricitinib (LY3009104) in Children With COVID-19 (COV-BARRIER-PEDS) (COV-BARRIER). Available at: https://clinicaltrials.gov/ct2/show/NCT05074420. Accessed 21 November 2021.
325.U.S. Food and Drug Administration. Highlights of Prescribing Information: XELJANZ® (tofacitinib) (package insert). Available at: https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/213082s000lbl.pdf. Accessed 11 August 2022.

Oral antivirals

Two new antiviral agents have been issued an EUA and include: nirmatrelvir/ritonavir and molnupiravir. Nirmatrelvir/ritonavir is not authorized in children younger than 12 years of age and weighing less than 40 kg [326]. However, there have been no safety or effectiveness studies in pediatric patients. Molnupiravir is not recommended for use in children due to animal studies that suggest effects on bone and cartilage growth.

Referenzen:
326. Hammond J, Leister-Tebbe H, Gardner A, et al. Oral Nirmatrelvir for High-Risk, Nonhospitalized Adults with Covid-19. N Engl J Med 2022; 386(15): 1397-408.

Monoclonal antibodies

At earlier stages in the pandemic, neutralizing monoclonal antibodies directed against the spike protein of SARS-CoV-2 have been used for pre- and post-exposure prophylaxis and treatment of individuals exposed to or infected with SARS-CoV-2 who are at high risk of progression to severe disease, but emergence of variants with in vitro reductions in susceptibility to these antibodies has left no available products in the United States. As noted previously, use of these products may be considered in areas of the world where a significant proportion of circulating variants retain susceptibility, taking into account the predicted relative benefits of the anti-SARS CoV-2 neutralizing antibody product compared with alternative antiviral therapies. In children, clinicians should also consider limitations in the age ranges and minimum body weight in which these products have been studied and should note that risk factors for progression to severe illness in children are less well-defined than in adults. Although risk-benefit ratios for the use of SARS-CoV-2 monoclonal

antibodies are likely similar between children and adults, pediatric-specific data are limited or lacking for all neutralizing monoclonal antibody products.

Treatments not recommended for use

As noted in other sections of this document, several interventions have been tested in adult populations and not found to have clinical benefit. This has led to recommendations against the routine use of hydroxychloroquine, lopinavir/ritonavir, inpatient convalescent plasma, and famotidine. Although the studies informing these recommendations largely excluded children with acute infection, the experience in adult patients suggests that these drugs would not be expected to have benefit in treatment of children with similar disease characteristics.

National COVID-19 Clinical Evidence Taskforce, 2023 [4].

Australian guidelines for the clinical care of people with COVID-19: version 74.1

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

Version 74.1 published on 30.5.2023

- Repräsentatives Gremium: **trifft zu**
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**
- 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:

- Ständige Aktualisierung: Stand: Effective Date: April 1, 2020
- Keine Information identifiziert, wann die letzte Recherche lief
- Letzte Aktualisierung: 30.05.2023

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 evidence suggests 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.

Empfehlungen

7.1 Recommended drug treatments

7.1.1 Casirivimab plus imdevimab (Ronapreve)

7.1.1.1 Casirivimab plus imdevimab (Ronapreve) for adults

Not recommended

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

Konsentierte Empfehlung

Do not routinely use casirivimab plus imdevimab (Ronapreve) for the treatment of COVID-19.

The Taskforce has previously recommended the use of casirivimab plus imdevimab (Ronapreve) for the treatment of individuals with COVID-19. Recommendations for individuals not requiring hospitalisation were based on three studies that included 6622 participants with mild COVID-19 [320][367][400], which demonstrated a benefit with regards to hospitalisation and adverse events. Recommendations for hospitalised individuals were based on two studies that included 10982 participants with moderate to severe COVID-19 [415][520], which demonstrated a benefit with regards to all-cause mortality at 28 days and serious adverse events.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab (Ronapreve) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective in treating individuals with currently circulating variants of COVID-19.

7.1.1.3 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Konsentierte Empfehlung

Do not routinely use casirivimab plus imdevimab (Ronapreve) in children and adolescents with COVID-19.

The Taskforce has previously only recommended the use of casirivimab plus imdevimab (Ronapreve) in exceptional circumstances for seronegative children and adolescents aged 12 years and over and weighing at least 40 kg who are at high risk of disease progression. Recommendations were based on indirect evidence from three studies of 6622 non-hospitalised participants with mild COVID-19 [320][367][400] that excluded children and adolescents, but which demonstrated a benefit with regards to hospitalisation and adverse events. Recommendations for hospitalised children and adolescents were based on two studies that included 10982 participants with moderate to severe COVID-19 [415][520], which demonstrated a benefit with regards to all-cause mortality at 28 days and serious adverse events.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of casirivimab plus imdevimab (Ronapreve) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that casirivimab plus imdevimab (Ronapreve) is effective in treating children and adolescents with currently circulating variants of COVID-19.

Referenzen

[320] Weinreich D, Sivapalasingam S, Norton T. REGEN-COV antibody cocktail in outpatients with COVID-19. medRxiv 2021. Journal Webseite

[367] Weinreich DM, Sivapalasingam S, Norton T, Ali S, Gao H, Bhore R, et al. REGEN-COV antibody combination and outcomes in outpatients with Covid-19. New England Journal of Medicine 2021. Pubmed Journal

[400] O'Brien MP, Forleo-Neto E, Sarkar N, Isa F, Hou P, Chan K-C, et al. Effect of subcutaneous casirivimab and imdevimab antibody combination vs placebo on development of symptomatic COVID-19 in early asymptomatic SARS-CoV-2 infection: A randomized clinical trial. JAMA 2022. Pubmed Journal

Nur in der Forschung

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

Additional information

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** children and adolescents hospitalised with moderate-to-critical COVID-19.

Additional information

In patients hospitalised with moderate-to-critical COVID-19 who are seropositive (detectable SARS-CoV-2 antibodies), casirivimab plus imdevimab (Ronapreve) probably has little impact on risk of death, 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.

7.1.2 Corticosteroids (inhaled)

7.1.2.1 Corticosteroids (inhaled) for adults

Conditional recommendation

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

7.1.2.2 Corticosteroids (inhaled) for children and adolescents

Conditional recommendation

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

Additional information

In adults with confirmed COVID-19 who do not require oxygen, inhaled corticosteroids probably reduce hospitalisation. In adults who are subsequently hospitalised due to disease progression, inhaled corticosteroids probably decrease the requirement for supplemental oxygen if taken within 14 days of onset of symptoms.

Results are primarily based on the PRINCIPLE trial [359], in which adults were treated with inhaled budesonide (by breath-actuated inhaler) 800 µg twice daily for up to 14 days. No children or adolescents were included in the trial.

Based on international cohort studies [370], risk factors for disease severity in children include:

- Paediatric Complex Chronic Conditions: congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

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.

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.

Referenzen:

[157] Ramakrishnan S, Nicolau DV, Langford B, Mahdi M, Jeffers H, Mwasuku C, et al. Inhaled budesonide in the treatment of early COVID-19 (STOIC): a phase 2, open-label, randomised controlled trial. Lancet Respiratory Medicine 2021. Pubmed Journal

[359] Yu L-M, Bafadhel M, Dorward J, Hayward G, Saville BR, Gbinigie O, et al. Inhaled budesonide for COVID-19 in people at high risk of complications in the community in the UK (PRINCIPLE): a randomised, controlled, open-label, adaptive platform trial. Lancet 2021;398(10303):843-855. Pubmed Journal

[419] [Intervention] for [COVID-19]..

[426] Clemency BM, Varughese R, Gonzalez-Rojas Y, Morse CG, Phipatanakul W, Koster DJ, et al. Efficacy of inhaled Ciclesonide for outpatient treatment of adolescents and adults with symptomatic COVID-19: a randomized clinical trial. JAMA Internal Medicine 2022;182(1):42-49. Pubmed Journal

[427] Ezer N, Belga S, Daneman N, Chan A, Smith BM, Daniels S-A, et al. Inhaled and intranasal ciclesonide for the treatment of covid-19 in adult outpatients: CONTAIN phase II randomised controlled trial. BMJ 2021;375:e068060. Pubmed Journal

[428] Song J-Y, Yoon J-G, Seo Y-B, Lee J, Eom J-S, Lee J-S, et al. Ciclesonide inhaler treatment for mild-to-moderate COVID-19: a randomized, open-label, phase 2 trial. Journal of Clinical Medicine 2021;10(16). Pubmed Journal

7.1.3 Corticosteroids (systemic)

7.1.3.1 Corticosteroids (systemic) for adults

Recommended

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

Bedingte Empfehlung gegen

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

7.1.3.3 Corticosteroids (systemic) for children and adolescents

Conditional recommendation

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

Additional information

A dose of 6 mg daily is recommended in adults. The RECOVERY trial protocol stated a dose of 0.15 mg/kg/day to a maximum of 6 mg/day for children but it is unclear whether any children were included in the trial. If dexamethasone is not available, an acceptable alternative regimen would be:

- hydrocortisone: intravenous or intramuscular 1 mg/kg/dose, every 6 hours for up to 10 days (to a maximum dose of 50 mg every 6 hours)
- methylprednisolone may also be an acceptable alternative, however the most appropriate dosage is uncertain

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

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.

Bedingte Empfehlung gegen

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

Additional information

Dexamethasone and other corticosteroids should still be used for other evidence-based indications in children and adolescents who have COVID-19.

For specific recommendations on the use of corticosteroids for PIMS-TS see section.

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.

7.1.4 Molnupiravir (Lagevrio)

7.1.4.1 Molnupiravir (Lagevrio) for adults

Bedingte Empfehlung gegen

Do not routinely use molnupiravir for the treatment of COVID-19.

7.1.4.3 Molnupiravir (Lagevrio) for children and adolescents

Nur in der Forschung

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

Additional information

Currently, there is no direct evidence for the use of molnupiravir (Lagevrio) in children and adolescents. Trials are needed in special populations, including children and adolescents. Until further evidence is available, do not routinely use molnupiravir for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Animal studies have shown potential deleterious effects on cartilage and bone growth, and it is unclear if these effects are reversible.

Currently molnupiravir is not approved for use in people under 18 years of age.

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

7.1.5 Nirmatrelvir plus ritonavir (Paxlovid)

7.1.5.1 Nirmatrelvir plus ritonavir (Paxlovid) for adults

Conditional recommendation

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

Within the patient population for which nirmatrelvir plus ritonavir is conditionally recommended for use (see Additional information), decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of nirmatrelvir plus ritonavir is unclear in individuals who have received any COVID-19 vaccine. See consensus recommendation for guidance on use of nirmatrelvir plus ritonavir in vaccinated adults or in immunocompromised patients regardless of vaccination status.*

Konsentierte Empfehlung

In addition to at-risk unvaccinated adults, also consider using nirmatrelvir plus ritonavir within 5 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors.

7.1.5.3 Nirmatrelvir plus ritonavir (Paxlovid) for children and adolescents

Konsentierte Empfehlung

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

Consider using nirmatrelvir plus ritonavir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, or those who are immunocompromised regardless of vaccination / previous infection status. Do not routinely use nirmatrelvir plus ritonavir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.

Decisions about the appropriateness of treatment with nirmatrelvir plus ritonavir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and whether they have received a COVID-19 vaccine dose or had a SARS-CoV-2 infection in the past 6 months.

Additional information

Decisions to provide nirmatrelvir plus ritonavir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the benefits of nirmatrelvir plus ritonavir (Paxlovid) in specific subgroups of children and adolescents. 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 children and adolescents are most likely to benefit from nirmatrelvir plus ritonavir. Based on international cohorts [370], potential factors to consider in patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

There is no evidence evaluating the effectiveness of nirmatrelvir plus ritonavir in people who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, 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 nirmatrelvir plus ritonavir will be particularly valuable in people who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

There is no evidence on the effectiveness of nirmatrelvir plus ritonavir in immunocompromised children and adolescents. However, given the likely higher risk of deterioration in these patients, and the absence of reasons to believe otherwise, it is likely that nirmatrelvir plus ritonavir will be beneficial for immunocompromised patients.

Ritonavir is an inhibitor, inducer and substrate of many enzymes and transporters involved in drug disposition and metabolism. It is a strong inhibitor of CYP3A, reducing the hepatic metabolism and increasing the concentration of nirmatrelvir and other CYP3A substrates. Co-administration of nirmatrelvir-ritonavir is contraindicated with drugs that are highly dependent upon CYP3A for clearance where an elevated concentration may be dangerous (e.g. anti-arrhythmics, antipsychotics, statins, anti-inflammatories, anti-cancer drugs and anticoagulants). Co-administration is also contraindicated with potent CYP3A inducers (e.g. anti-epileptics, rifampin, St John's wort), which can reduce concentrations of nirmatrelvir and/or ritonavir, reducing efficacy and increasing resistance. Induction persists many days after cessation due to time required for clearance of the inducing drug and of the induced CYP3A.

Evidence demonstrates a likely weak interaction between nirmatrelvir-ritonavir and budesonide, resulting in increased budesonide concentrations. There are no other expected interactions between nirmatrelvir-ritonavir and other therapeutics currently recommended for the treatment of COVID-19 within the Taskforce guidelines. It is crucial that consideration is given to the potential for complex, serious drug-drug interactions when prescribing and administering nirmatrelvir plus ritonavir with other medications (see Liverpool interaction checker and TGA PI).

Available data suggests that administering nirmatrelvir plus ritonavir as an oral suspension does not alter its pharmacokinetic parameters (Liverpool University). Although the swallowing of whole tablets remains the preferred method of administration where necessary, nirmatrelvir plus ritonavir tablets can be crushed or split and mixed with food or liquid, or alternatively administered via nasogastric tube, as indicated.

In the absence of clinical data in paediatric populations, it is particularly important to ensure that any adverse events are appropriately reported.

As of 9 May 2022, the Therapeutic Goods Administration has not approved nirmatrelvir plus ritonavir for this indication. In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

Nirmatrelvir plus ritonavir is currently listed within the Australian Pharmaceutical Benefits Scheme. Details can be found here.

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

Nur in der Forschung

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

Additional information

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

7.1.6 Other immunomodulating drugs

Information

The Taskforce has developed conditional recommendations supporting the use of several non-steroidal immunomodulatory agents for the treatment of COVID-19 in hospitalised patients requiring supplemental oxygen. All of these treatments demonstrate a mortality benefit when used in this patient population (moderate certainty of evidence). While the RECOVERY trial suggests a benefit when using baricitinib in conjunction with corticosteroids, tocilizumab or remdesivir [521], the Taskforce notes that concomitant use of two or more of these immunomodulatory agents may increase the risk of side effects such as opportunistic infection.

All studies that contribute data to analyses underpinning these recommendations compare the treatment of interest with either standard care or placebo. In the absence of data directly comparing one agent to another, it is unclear which of these agents is clinically superior, and thus it is not possible to promote the use of one treatment over another as first line therapy based on clinical evidence alone.

The Taskforce acknowledges the importance of other factors in deciding which treatment is administered, such as availability (e.g. sarilumab has not been approved by the TGA), route of administration and cost. A table providing a comparison of clinical and non-clinical factors between the three recommended immunomodulators can be found here.

7.1.6.1 Abatacept

7.1.6.1.1 Abatacept for adults

Conditional recommendation

Consider using abatacept for the treatment of COVID-19 in adults who require supplemental oxygen but not mechanical ventilation or ECMO, particularly where there is evidence of systemic inflammation.

7.1.6.2 Baricitinib

7.1.6.2.1 Baricitinib for adults

Conditional recommendation

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

7.1.6.2.3 Baricitinib for children and adolescents

Konsentierte Empfehlung

Consider using baricitinib for the treatment of COVID-19 in children and adolescents who require non-invasive or invasive ventilation.

Additional information

In adult patients hospitalised with COVID-19 who require supplemental oxygen, baricitinib probably reduces the risk of death. Although there is a paucity of safety data regarding the use of baricitinib in paediatric patients, the Taskforce notes that the RECOVERY trial included 33 patients 2–18 years of age in their analyses [521]. Because of this, the Taskforce gives a consensus recommendation for baricitinib use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections).

Baricitinib should be administered orally, either as a tablet or dissolved in 10–15 ml of water. Alternatively, if the patient is unable to swallow, baricitinib can be administered via nasogastric feeding tube, however, it may block tubes that are size 12 French or smaller. Do not crush or disperse the tablet if you are pregnant: staff who are actively trying to conceive or who are pregnant or breastfeeding should not prepare or handle a dispersed dose (NSW TAG). If cutting the tablet it should be done in a powder containment cabinet OR may be cut using a tablet cutter if wearing full PPE [457].

Following protocol information in the RECOVERY trial, the suggested dose is dependent on age:

- Children 2–9 years: 2 mg per day
- Children 10–18 years: 4 mg per day

In addition, the RECOVERY trial demonstrated a significant benefit when using corticosteroids in conjunction with baricitinib in adults. Use of combined baricitinib and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require non-invasive or invasive ventilation, however, the optimal sequencing of baricitinib and corticosteroid use is unclear in all populations.

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

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

7.1.6.3 Infliximab

7.1.6.3.1 Infliximab for adults

Conditional recommendation

Consider using infliximab for the treatment of COVID-19 in adults who require supplemental oxygen but not mechanical ventilation or ECMO, particularly where there is evidence of systemic inflammation.

7.1.6.4 Sarilumab

7.1.6.4.1 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.

7.1.6.4.3 Sarilumab for children and adolescents

Nur in der Forschung

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

Additional information

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.

7.1.6.5 Tocilizumab

7.1.6.5.1 Tocilizumab for adults

Conditional recommendation

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

7.1.6.5.3 Tocilizumab for children and adolescents

Conditional recommendation

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

Additional information

In adult 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 use both within and outside the context of a randomised trial unless contraindicated (e.g. patients with other active, severe infections). No children were enrolled in any of the trials included.

There is no established dose for tocilizumab for the treatment of acute COVID-19 in children or adolescents. (The Taskforce notes that RECOVERY is recruiting children and adolescents with PIMS-TS for their trial of tocilizumab [74].) Tocilizumab should be administered as a single intravenous infusion over 60 minutes. Following protocol information in the RECOVERY trial, as well as previous literature on the use of tocilizumab for other indications, the suggested dose is dependent on body weight:

- Infants < 1 year (excluded from RECOVERY trial): dosing from other uses 12 mg/kg [73]
- < 30 kg: 12 mg/kg
- ≥ 30 kg: 8 mg/kg (max 800 mg)

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 in adults. Use of combined tocilizumab and corticosteroids should be considered in children and adolescents hospitalised with COVID-19 who require oxygen, however, the optimal sequencing of tocilizumab and corticosteroid use is unclear in all populations.

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.

7.1.7 Regdanvimab (Regkirona)

7.1.7.1 Regdanvimab (Regkirona) for adults

Konsentierte Empfehlung

Do not routinely use regdanvimab (Regkirona) for the treatment of COVID-19.

The Taskforce has previously recommended the use of regdanvimab (Regkirona) for the treatment of individuals with COVID-19 who do not require oxygen. These recommendations were based on a sequential trial (parts 1 and 2) [499][585] that included 1629 unvaccinated participants with mild COVID-19, which demonstrated a benefit with regards to hospitalisation, supplemental oxygen and clinical recovery.

All clinical trials that contributed data to the analyses were conducted prior to the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of regdanvimab (Regkirona) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that regdanvimab (Regkirona) is effective in treating individuals with currently circulating variants of COVID-19.

7.1.7.3 Regdanvimab (Regkirona) for children and adolescents

Nur in der Forschung

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

Additional information

Currently, there is no direct evidence evaluating the effectiveness of regdanvimab (Regkirona) in children and adolescents. Until further evidence is available, do not use regdanvimab for the treatment of COVID-19 in children and adolescents unless they are eligible to be enrolled in trials.

Currently regdanvimab is not approved for use in people under 18 years of age.

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

7.1.8 Remdesivir (Veklury)

7.1.8.1 Remdesivir (Veklury) for adults

Conditional recommendation

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

Not recommended

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

Conditional recommendation

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

Within the patient population for which remdesivir is conditionally recommended for use (see Additional information), decisions about the appropriateness of remdesivir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and vaccination status (including number of doses and time since last dose/ or timing of most recent infection).

** Individuals who had received one or more doses of SARS-CoV-2 vaccine were excluded from the trial. The efficacy of remdesivir is unclear in individuals who have received any COVID-19 vaccine. See consensus recommendation for guidance on use of remdesivir in vaccinated adults or in immunocompromised patients regardless of vaccination status.*

Konsentierte Empfehlung

In addition to at-risk unvaccinated adults, also consider using remdesivir within 7 days of symptom onset in adults with COVID-19 who do not require oxygen and are immunocompromised; or are at particularly high risk of severe disease on the basis of advanced age and multiple risk factors.

7.1.8.3 Remdesivir (Veklury) for children and adolescents

Information

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines).*

Konsentierte Empfehlung

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 within 7 days of symptom onset in **children and adolescents aged 28 days and over and weighing at least 3 kg** who do not require oxygen and are at high risk of deterioration, where other treatments are not available / appropriate.

Consider using remdesivir in eligible children and adolescents who have not received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, those who are immunocompromised regardless of vaccination / previous infection status, or those who are not eligible for vaccination based on age but who are at high risk of disease progression. Do not routinely use remdesivir in children and adolescents who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months unless immunocompromised.

Decisions about the appropriateness of treatment with remdesivir should be based on the individual's risk of severe disease, including their age, presence of multiple risk factors, and whether they have received a COVID-19 vaccine dose or had a SARS-CoV-2 infection in the past 6 months.

Additional information

Please note:

1. Remdesivir (Veklury) is not TGA approved for mild disease in children < 40 kg

2. There are potential concerns with the use of cyclodextrin in infants, so the benefits and risks should be carefully assessed

Decisions to provide remdesivir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the potential benefits and risks of remdesivir in specific subgroups of children and adolescents. 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 children and adolescents are most likely to benefit from remdesivir. Based on international cohorts [370] potential factors to consider in patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

There is no evidence evaluating the effectiveness of remdesivir 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 remdesivir will be particularly valuable in patients who have received a vaccine dose or had a SARS-CoV-2 infection in the past 6 months, unless the patient is immunocompromised.

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

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

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

Referenzen:

[414] Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early remdesivir to prevent progression to severe Covid-19 in outpatients. New England Journal of Medicine 2022;386(4):305-315.

Konsentierte Empfehlung

Consider using, in exceptional circumstances, remdesivir for the treatment of COVID-19 in **children and adolescents aged 28 days or older and weighing at least 3 kg** who are hospitalised with severe COVID-19 (considered likely to progress to ventilation), who require systemic corticosteroids and oxygen but do not require non-invasive or invasive ventilation, where other treatments are not available / appropriate.

Additional information

Please note:

1. Remdesivir (Veklury) is not TGA approved for mild disease in children < 40 kg

2. There are potential concerns with the use of cyclodextrin in infants, so the benefits and risks should be carefully assessed

Decisions to provide remdesivir to a child or adolescent should be based on the individual's combination of risk factors for deterioration and be made in consultation with a paediatrician with expertise in the management of COVID-19 in children.

Available research does not currently provide enough evidence to determine the potential benefits and risks of remdesivir in specific subgroups of children and adolescents. 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 children and adolescents are most likely to benefit from remdesivir. Based on international cohorts [370] potential factors to consider in patients at high risk of progression may include:

- Paediatric Complex Chronic Conditions (PCCC): congenital and genetic, cardiovascular, gastrointestinal, malignancies, metabolic, neuromuscular, renal and respiratory conditions
- Severe asthma
- Obesity

In the absence of reliable evidence, the Taskforce has developed this recommendation based on their clinical expertise and experience.

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

Not recommended

Do not start Remdesivir in children and adolescents hospitalised with COVID-19 who require non-invasive or invasive ventilation.

Additional information

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

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

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.

7.1.9 Sotrovimab (Xevudy)

7.1.9.1 Sotrovimab (Xevudy) for adults

Konsentierte Empfehlung

Do not routinely use sotrovimab (Xevudy) for the treatment of COVID-19.

The Taskforce has previously recommended the use of sotrovimab (Xevudy) for the treatment of unvaccinated individuals with COVID-19 who do not require oxygen and who have one or more risk factors for disease progression. These recommendations were based on the COMET-ICE trial [439] that included 1057 participants with mild-to-moderate COVID-19, which demonstrated a benefit with regards to hospitalisation.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of sotrovimab (Xevudy) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that sotrovimab (Xevudy) is effective in treating individuals with currently circulating variants of COVID-19.

7.1.9.3 Sotrovimab (Xevudy) for children and adolescents

Information

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines)*.

Konsentierte Empfehlung

Do not routinely use sotrovimab (Xevudy) for the treatment of COVID-19 in children.

The Taskforce has previously only recommended the use of sotrovimab for the treatment of children aged over 12 years and over 40 kg in exceptional circumstances who do not require oxygen and who are at high risk of deterioration. These recommendations were based on indirect evidence from the COMET-ICE trial [439] that included 1057 participants with mild-to-moderate COVID-19, which demonstrated a benefit with regards to hospitalisation.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of sotrovimab (Xevudy) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that sotrovimab (Xevudy) is effective in treating individuals with currently circulating variants of COVID-19.

Referenzen:

[439] Gupta A, Gonzalez-Rojas Y, Juarez E, Crespo Casal M, Moya J, Rodrigues Falci D, et al. Effect of sotrovimab on hospitalization or death among high-risk patients with mild to moderate COVID-19: a randomized clinical trial. JAMA 2022.

Nur in der Forschung

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

Where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab should only be considered where other treatments are not suitable or available.

Additional information

Where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab in children and adolescents should only be considered where other treatments are not suitable or available. There are limited evidence-based alternatives for children and adolescents currently (e.g. inhaled corticosteroids)

While the clinical evidence supports use of sotrovimab to treat mild COVID-19 (in adults at high risk of severe disease), there is no clinical evidence to evaluate its effectiveness against the Omicron variant or BA.1, BA.2, BA.4 or BA.5 sub-variants. The Taskforce is aware of in vitro *data that suggest potentially reduced efficacy against these variants and while the clinical implications of this are not certain, given the availability of other treatments, where infection with Omicron BA.2, BA.4 or BA.5 is confirmed or considered likely, use of sotrovimab should not be considered unless other treatments are unsuitable or unavailable.*

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

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

Specific sub-populations may be considered for treatment with sotrovimab, such as children over 12 years with a high risk of deterioration (see recommendation below).

7.1.10 Tixagevimab plus cilgavimab (Evusheld)

7.1.10.1 Tixagevimab plus cilgavimab (Evusheld) for adults

Konsentierte Empfehlung

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19.

The Taskforce has previously recommended the use of tixagevimab plus cilgavimab (Evusheld) for the treatment of individuals with COVID-19 who do not require mechanical ventilation. Recommendations for those not requiring oxygen were based on the TACKLE trial [519] that included 903 unvaccinated adults with mild COVID-19, which demonstrated a benefit with regards to progression to severe COVID-19, adverse events and hospitalisation. Recommendations for those requiring oxygen were based on the ACTIV-3-TICO trial [502] that included 1088 predominately unvaccinated individuals, which demonstrated a benefit with regards to all-cause mortality at 28 and 90 days.

All clinical trials that contributed data to the analyses were conducted before the emergence of Omicron as the dominant variant. Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective in treating individuals with currently circulating variants of COVID-19. Use maybe considered for known Omicron BA2 as *in vitro* evidence suggests that some efficacy remains for this variant.

Nur in der Forschung

Do not use tixagevimab plus cilgavimab for the treatment of COVID-19 in adults who require mechanical ventilation outside of randomised trials with appropriate ethical approval.

7.1.10.3 Tixagevimab plus cilgavimab (Evusheld) for children and adolescents

Information

Children and adolescents who are suspected to be at high risk of deterioration should be managed by and discussed with a multidisciplinary team. Decisions about exceptional use of treatments outside the recommendations made by the Taskforce should be taken in consultation with experts, in the light of the potential for rapid deterioration, with appropriate involvement of hospital drug and therapeutics committee and awareness of the CATAG guidance for off-label use of medications *(see CATAG guiding principles for the quality use of off label medicines)*.

Konsentierte Empfehlung

Do not routinely use tixagevimab plus cilgavimab (Evusheld) for the treatment of COVID-19 in children and adolescents.

The Taskforce has previously only recommended the use of tixagevimab plus cilgavimab (Evusheld) in exceptional circumstances for the treatment of COVID-19 in children and adolescents aged 12 years and over and weighing at least 40 kg who were at high risk of deterioration but did not require mechanical ventilation. This was due to no direct evidence being available to inform it use.

Since the development of the initial recommendations, a significant body of *in vitro* evidence has emerged demonstrating a significant reduction in activity of tixagevimab plus cilgavimab (Evusheld) against the Omicron BA.4, BA.5 and newer sub-variants (including recombinant variants such as XBB and XBF). As a result, it is unlikely that tixagevimab plus cilgavimab (Evusheld) is effective in treating individuals with currently circulating variants of COVID-19. Use may be considered for known Omicron BA2 as *in vitro* evidence suggests that some efficacy remains for this variant.

Nur in der Forschung

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

Additional information

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

7.2 Drug treatments that are not recommended:

- Aspirin
- Azithromycin
- Colchicine
- Convalescent plasma
- Favipiravir
- Hydroxychloroquine
- Hydroxychloroquine plus azithromycin
- Interferon beta-1a
- Interferon beta-1a plus lopinavir-ritonavir
- Ivermectin
- Lopinavir-ritonavir

Drug treatments not recommended outside of clinical trials

Treatment category	Treatment
Antiandrogens	Dutasteride
Antineoplastics	Angiotensin 2 receptor agonist (C21) Camostat mesilate Opaganib
Antiparasitic, antifungals and other anti-infective agents	Chloroquine Doxycycline Ivermectin plus doxycycline Nitazoxanide
Antihypertensives	Telmisartan
Antithrombotic, antiplatelets and related therapies	Sulodexide
Antivirals	Baloxavir marboxil Darunavir-cobicistat Enisamium Ensovibep Sofosbuvir-daclatasvir Triazavirin Umifenovir
Human and blood derived products	Human umbilical cord mesenchymal stem cells Intravenous immunoglobulin Intravenous immunoglobulin plus methylprednisolone
	Anakinra CD24Fc
Immunomodulating drugs	Lenzilumab Ruxolitinib Tofacitinib
Interferons	Interferon beta-1a (inhaled) Interferon beta-1b Interferon gamma Interferon kappa plus trefoil factor 2 (IFN-κ plus TFF2) Peginterferon lambda
Other antibody related therapies	Bamlanivimab Bamlanivimab plus etesevimab Bebtelovimab
Other therapies	Almitrine Aprepitant Bromhexine hydrochloride Fluvoxamine Metformin Recombinant human granulocyte colony-stimulating factor Sabizabulin
Vitamins, supplements and cofactors	Combined metabolic activators (CMA) N-acetylcysteine Vitamin C Vitamin D analogues (calcifediol / cholecalciferol) Zinc

7.3.1. Other drug treatments

Konsentierte Empfehlung

For people with COVID-19, do not use other drug treatments outside of randomised trials with appropriate ethical approval.

Additional information

Trials are needed in special populations, including children and adolescents, pregnant and breastfeeding women, older people living with frailty and those receiving palliative care. Until further evidence is available, do not use other drug treatments in these populations unless they are eligible to be enrolled in trials.

World Health Organization (WHO), 2023 [6].

Therapeutics and COVID-19: Living Guideline; Version 14

Zielsetzung/Fragestellung

The WHO Therapeutics and COVID-19: living guideline contains the most up-to-date recommendations for the use of therapeutics in the treatment of COVID-19.

Hinweis: In der Leitlinie sind keine spezifischen Empfehlungen für Kinder enthalten. Falls besondere Hinweise für die pädiatrische Population vorhanden sind werden diese mitextrahiert.

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: **trifft zu**.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: **trifft zu**.
- 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:

- *Hinweis: This guideline is living – dynamically updated and globally disseminated once new evidence warrants a change in recommendations.*
- Leitlinie basiert auf systematischem (Living) Review (Siemieniuk RAC, Bartoszko JJ, Zeraatkar D, Izcovich A, Pardo-Hernandez H, Rochwerg B, et al. Drug treatments for covid-19: living systematic review and network meta-analysis [Update 6]. BMJ 2023;370::m2980), fünfte Version
- Daily searches from Monday to Friday in the World Health Organization (WHO) covid-19 database for eligible studies
- 25 bibliographic and grey literature sources: Medline (Ovid and PubMed), PubMed Central, Embase, CAB Abstracts, Global Health, PsycInfo, Cochrane Library, Scopus, Academic Search Complete, Africa Wide Information, CINAHL, ProQuest Central, SciFinder, the Virtual Health Library, LitCovid, WHO covid-19 website, CDC covid-19

website, Eurosurveillance, China CDC Weekly, Homeland Security Digital Library, ClinicalTrials.gov, bioRxiv (preprints), medRxiv (preprints), chemRxiv (preprints), and SSRN (preprints)

- Six Chinese databases: Wanfang, Chinese Biomedical Literature, China National Knowledge Infrastructure, VIP, Chinese Medical Journal Net (preprints), and ChinaXiv (preprints) (Bis 20. Februar 2021)
- Suche in den englischsprachigen Informationsquellen vom 1. Dezember 2019 bis zum 3. December 2021
- Suche in den chinesischsprachigen Informationsquellen bis 20. Februar 2021
- Letzte Aktualisierung: 14. Juli 2022

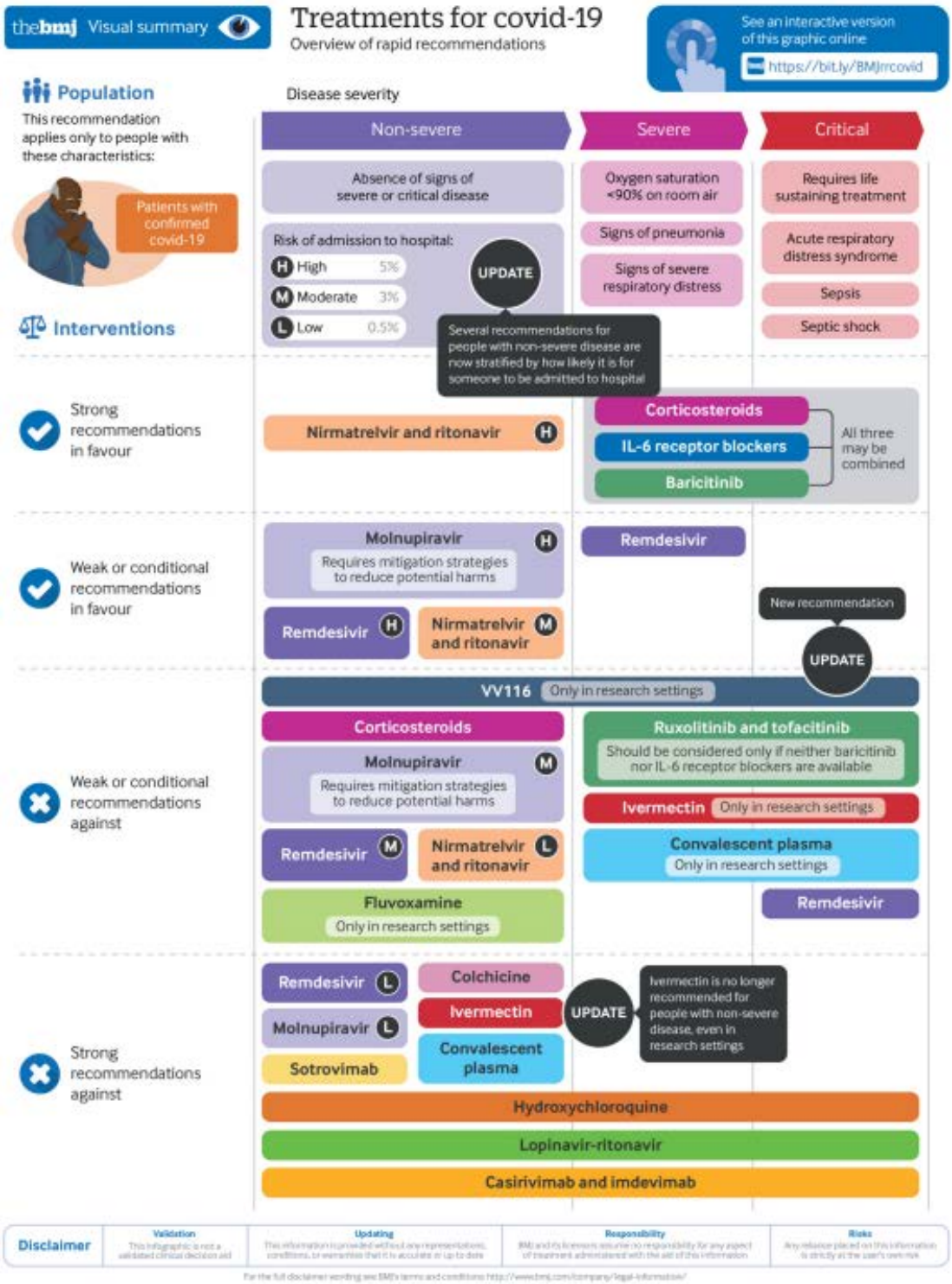
LoE

- GRADE

GoR

- Strong recommendations: Strong recommendations communicate the message that the guideline is based on the confidence that the desirable effects of adherence to the recommendation outweigh the undesirable consequences. Strong recommendations are uncommon because the balance between the benefits and harms of implementing a recommendation is rarely certain. In particular, GDGs need to be cautious when considering making strong recommendations on the basis of evidence whose quality is low or very low.
- Conditional or weak recommendations: Recommendations that are conditional or weak are made when a GDG is less certain about the balance between the benefits and harms or disadvantages of implementing a recommendation. Conditional recommendations generally include a description of the conditions under which the end-user should or should not implement the recommendation.

Recommendations for patients with non-severe COVID-19



Last update: 10. November 2025

Nirmatrelvir-ritonavir (updated 10 November 2023)

For patients with non-severe COVID-19 at high risk of hospitalization we recommend treatment with nirmatrelvir-ritonavir (**strong recommendation for**).

For patients with non-severe COVID-19 at moderate risk of hospitalization we suggest to use treatment with nirmatrelvir-ritonavir (conditional recommendation for).

For patients with non-severe COVID-19 at low risk of hospitalization we suggest not to use nirmatrelvir-ritonavir (conditional recommendation against).

Remdesivir (updated 10 November 2023)

For patients with non-severe COVID-19 at high risk of hospitalization we suggest treatment with remdesivir (conditional recommendation for).

The GDG concluded that nirmatrelvir-ritonavir may represent a superior choice to remdesivir because of the practical difficulty that arises from the intravenous administration of remdesivir. Remdesivir is likely to be the desirable option in patients for whom nirmatrelvir-ritonavir or molnupiravir are not options. For nirmatrelvir, this will be patients who are using drugs with problematic interactions with nirmatrelvir-ritonavir. For molnupiravir, these will be individuals in whom concerns regarding mutagenesis are particularly great, which would include pregnancy and children. For both drugs, it will include those for whom, for whatever reason, the drugs are unavailable.

The GDG noted that there is insufficient evidence to make a recommendation around the use of remdesivir in children and further studies are needed. Additionally, the trials did not enrol pregnant or breastfeeding individuals. The decision regarding use of this therapeutic should be made between the pregnant person and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and WHO information sheet).

Only one of the trials included children (12 years of age and older), and the numbers were extremely small; **therefore the applicability of this recommendation to children remains uncertain**. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and Practical info tabs).

In patients with non-severe COVID-19 at high risk of hospitalization, remdesivir probably results in 44 fewer admissions per 1000 patients (95% CI 56 fewer to 9 fewer), with probably little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain. The planned subgroup analyses for remdesivir versus standard care including age, time of symptom onset and disease severity could not be performed in the absence of subgroup data reported publicly or provided by investigators. There were eight children (12 years or more of age) enrolled in the PINETREE trial [29]; none died or were hospitalized. Relative to both nirmatrelvir/ritonavir and molnupiravir, there is little or no difference in mortality. Remdesivir may reduce admission to hospital more than molnupiravir; there may be little or no difference when compared to nirmatrelvir-ritonavir.

For patients with non-severe COVID-19 at moderate risk of hospitalization we suggest not to use remdesivir (conditional recommendation against).

The GDG concluded that nirmatrelvir-ritonavir represents a superior choice because it is easier to administer than a 3- day course of intravenous remdesivir. The conditional recommendation against represents the panel's view that remdesivir will represent a good choice only in those in whom nirmatrelvir-ritonavir is unavailable or involves problematic interactions, and even then only in a minority of such individuals.

In patients with non-severe COVID-19 at moderate risk of hospitalization, remdesivir probably results in 22 fewer admissions per 1000 patients (95% CI 28 fewer to 4 fewer) with probably little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain. The planned subgroup analyses for remdesivir versus standard care including age, time of symptom onset and disease severity could not be performed in the absence of subgroup data reported publicly or provided by investigators. There were eight children (12 years or more of age) enrolled in the PINETREE trial [31]; none died or were hospitalized. Relative to nirmatrelvir-ritonavir, there is little or no difference in mortality with remdesivir and may be little or no difference in admission to hospital. Relative to molnupiravir, there is little or no difference in mortality with remdesivir. Molnupiravir may reduce admission to hospital compared with remdesivir in patients at high and moderate risk of hospitalization.

For patients with non-severe COVID-19 at low risk of hospitalization we recommend not to use remdesivir (strong recommendation against).

The marginal benefits of remdesivir for patients at low risk of hospitalization (those expected to have a 0.5% risk of hospital admission) suggest most patients would not want to use this treatment. Given considerations regarding resources and equity, the GDG concluded that health care systems may reasonably not offer this drug to patients at low risk of hospitalization.

In patients with non-severe COVID-19 at low risk of hospitalization, remdesivir does not result in important reductions in admissions and probably has little or no impact on mortality, mechanical ventilation and time to symptom resolution. The impact on adverse events leading to discontinuation is uncertain (absolute risk difference 4 more per 1000 [CI 95% 0 more to 17 more]).

The evidence summary was informed by seven trials with 5138 patients with non-severe COVID-19 included in the updated NMA. All trials compared remdesivir with standard care, with or without a placebo. Only one trial with 584 patients enrolled outpatients [31], and the rest enrolled in-patients. Relative to standard of care, the GDG rated certainty of evidence as: moderate for decreased admission to hospital (due to serious imprecision), mortality and mechanical ventilation; and very low for adverse effects leading to drug discontinuation. Relative to both nirmatrelvir-ritonavir and molnupiravir, because of very low baseline risk, the GDG rated certainty in mortality with remdesivir as high. Due to very serious imprecision, admission to hospital was rated as low certainty.

Referenzen

31 Gottlieb RL, Vaca CE, Paredes R, Mera J, Webb BJ, Perez G, et al. Early Remdesivir to Prevent Progression to Severe Covid-19 in Outpatients. New Eng J Med 2022;386(4):305-315.

Molnupiravir (updated 10 November 2023)

For patients with non-severe COVID-19 at high risk of hospitalization we suggest treatment with molnupiravir (conditional recommendation for).

The applicability of this recommendation to children, breastfeeding and pregnant individuals is currently uncertain, as the included RCTs enrolled only non-pregnant adults. However, the GDG concluded that molnupiravir should not be offered to children, breastfeeding or pregnant individuals with COVID-19. In addition, men planning to conceive should be oriented on the potential for temporary genotoxic effect on sperm cell production. The unknown long-term risk of genotoxicity is likely to be higher in younger patients as compared with older patients, thus its use in younger adults not at high risk should be avoided.

For patients with non-severe COVID-19 at moderate risk of hospitalization We suggest against treatment with molnupiravir (conditional recommendation against).

For patients with non-severe COVID-19 at low risk of hospitalization We recommend against treatment with molnupiravir (strong recommendation against).

Systemic corticosteroids (published 2 September 2020)

For patients with non-severe COVID-19 we suggest not to use systemic corticosteroids (conditional recommendation against).

Fluvoxamine (published 14 July 2022)

For patients with non-severe COVID-19 we recommend not to use fluvoxamine, except in the context of a clinical trial (recommended only in research settings).

Sotrovimab (updated 13 January 2023)

For patients with non-severe COVID-19 we recommend against treatment with sotrovimab (strong recommendation against).

The GDG considered in vitro data demonstrating that neutralization of currently circulating variants of SARS-CoV-2 and their subvariants with sotrovimab is diminished. There was consensus among the panel that the meaningful reduction of in vitro neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab. There was also consensus regarding the need

for clinical trial evidence in order to confirm clinical effectiveness of new monoclonal antibodies that reliably neutralize circulating strains in vitro.

In light in vitro evidence, the GDG concluded that the clinical effects of sotrovimab for COVID-19 caused by the currently circulating variants and subvariants of SARS-CoV-2 are highly uncertain. The existing trial evidence identified in the LNMA [2] was judged to be at moderate certainty for reduced hospitalization and high certainty for absence of infusion reactions, with no or small differences in mortality or mechanical ventilation. With the new circulating SARS-CoV-2 variants, this trial evidence would be rated as very low, meaning that the benefits of sotrovimab cannot be determined by trials performed before the new variants occurred.

Referenzen

2 Siemieniuk RAC, Bartoszko JJ, Díaz Martinez JP, Kum E, Qasim A, Zeraatkar D, et al. Antibody and cellular therapies for treatment of covid-19: a living systematic review and network meta-analysis. BMJ 2021;374:n2231.

Colchicine (published 14 July 2022)

For patients with non-severe COVID-19 we recommend against treatment with colchicine (strong recommendation against).

Recommendations for patients with severe and critical COVID-19

Systemic corticosteroids (published 2 September 2020)

For patients with severe or critical COVID-19 we recommend treatment with systemic corticosteroids (strong recommendation for).

The applicability of the recommendation is less clear for populations that were under-represented in the considered trials, such as children, patients with tuberculosis, and those who are immunocompromised. Notwithstanding, clinicians will also consider the risk of depriving these patients of potentially life-saving therapy. In contrast, the panel concluded that the recommendation should definitely be applied to certain patients who were not included in the trials, such as patients with severe and critical COVID-19 who could not be hospitalized or receive oxygen because of resource limitations.

Interleukin-6 receptor blockers (published 6 July 2021)

For patients with severe or critical COVID-19 we recommend treatment with IL-6 receptor blockers (tocilizumab or sarilumab) (strong recommendation for).

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the GDG had no reason to think that children with COVID-19 would respond any differently to treatment with IL-6 receptor blockers. This is especially true given tocilizumab is used in children safely for other indications including polyarticular juvenile rheumatoid arthritis, systemic onset of juvenile chronic arthritis, and chimeric antigen receptor T-cell induced cytokine release syndrome. Sarilumab is not approved in children, so if an IL-6 receptor blocker is used in this population, tocilizumab is preferred. The GDG also recognized that in many settings children are commonly admitted to hospital with acute respiratory illnesses caused by other pathogens; as a result, it may be challenging to determine who is ill with severe COVID-19, even with a positive test, and therefore likely to benefit from IL-6 receptor blockade. There were similar considerations in regard to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. The drug may, however, cross the placental membrane, although it is uncertain what effect transient immunosuppression in the fetus may have and this should be weighed against the potential benefit for the pregnant individual.

Janus kinase inhibitors (updated 16 September 2022)

For patients with severe or critical COVID-19 We recommend treatment with baricitinib (strong recommendation for).

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to administration of baricitinib to pregnant or lactating individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and Practical info).

For patients with severe or critical COVID-19 we suggest not to use ruxolitinib or tofacitinib (conditional recommendation against).

None of the included RCTs enrolled children; therefore, the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to the administration of ruxolitinib or tofacitinib to pregnant or lactating individuals.

Remdesivir (updated 16 September 2022)

For patients with severe COVID-19 we suggest treatment with remdesivir (conditional recommendation for).

One should use caution when administering remdesivir to patients with significant liver or kidney disease. **The GDG noted that there is insufficient evidence to make a recommendation around use in children and further studies are needed.** Additionally, the trials did not enrol pregnant or breastfeeding individuals. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the pregnant individual and fetus (see Research evidence and WHO information sheet).

In patients with severe COVID-19, remdesivir possibly reduces mortality and probably reduces the need for mechanical ventilation and probably has little or no impact on time to symptom improvement. The drug was well tolerated and adverse events were rare. The GDG critically evaluated the credibility of the data for severe and critical subgroups and the need to make separate recommendations (see Justification). It was felt that remdesivir would have an important effect in the severe subgroup and a conditional recommendation could be made for this group. **Subgroup analysis based on age was not possible due to lack of trial level data. The GDG noted with concern the dearth of paediatric data and a strong call for research in this area was made.** The lack of data regarding the effect in immunocompromised patients was also highlighted. While there is limited evidence in vaccinated populations, the GDG felt that the data were sufficient to conditionally recommend the use of remdesivir. The timing of initiation of therapy was not well reported across the studies and there was no clear subgroup effect based on time.

Certainty of evidence was rated as: low for decreased mortality (rated down from high for imprecision and inconsistency given the ongoing uncertainty regarding credibility of the severity of illness subgroup effect modification); moderate for reduction in need for invasive mechanical ventilation; and moderate for little or no impact on time to symptom improvement.

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children remains uncertain. Uncertainty also remains with regard to administration of remdesivir to pregnant or lactating people. The decision regarding use of this therapeutic should be made between the pregnant individual and their health care provider while discussing whether the potential benefit justifies the potential risk to the mother and fetus (see Research evidence and Practical info). As the pandemic evolves, and similar to other COVID-19 interventions, there is ongoing uncertainty related to the effect of remdesivir based on variants and individual immune status.

For patients with critical COVID-19 we suggest not to use remdesivir (conditional recommendation against).

In patients with critical COVID-19, remdesivir possibly has little or no effect on mortality, need for mechanical ventilation and has an uncertain effect on time to symptom improvement. The drug was well tolerated and adverse events were rare. Subgroup analysis based on age was not possible due to lack of trial level data. The GDG considered the potential of small subgroup effects in immunocompromised patients and critically ill patients with prolonged detection of SARS-CoV-2 RNA in blood specimens; however, given the paucity of data and concerns for harm, it was felt that a conditional recommendation against the use of remdesivir was appropriate.

Certainty of evidence was rated as: low for no impact on mortality or invasive mechanical ventilation (rated down from high for imprecision and inconsistency given the ongoing uncertainty regarding credibility of

the severity of illness subgroup effect modification); and very low for no impact on time to symptom improvement.

None of the included RCTs enrolled children or pregnant individuals, and therefore the applicability of this recommendation to children remains uncertain. As the pandemic evolves, and similar to other COVID-19 interventions, there is ongoing uncertainty related to the effect of remdesivir based on variants and individual immune status.

Recommendations against therapeutics applicable across disease severities

VV116 (published 10 November 2023)

For patients with COVID-19, regardless of disease severity we recommend not to use VV116, except in the context of a clinical trial (recommended only in research settings).

The included RCTs did not enrol children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with VV116. There were similar considerations for pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Ivermectin (updated 10 November 2023)

For patients with non-severe COVID-19 we recommend not to use ivermectin strong recommendation against).

Subgroup analyses indicated no effect modification based on dose. **We were unable to examine subgroups based on patient age or severity of illness due to insufficient trial data** (see Research evidence), and similar effects were inferred for all subgroups.

For patients with severe or critical COVID-19 we recommend not to use ivermectin, except in the context of a clinical trial (recommended only in research settings).

None of the included RCTs enrolled children under 15, and **therefore the applicability of this recommendation to children is currently uncertain**. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with ivermectin. There were similar considerations for pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently to other adults.

Convalescent plasma (published 7 December 2021)

For patients with non-severe COVID-19 we recommend against treatment with convalescent plasma (strong recommendation against).

The applicability of this recommendation to children or pregnant individuals is currently uncertain, as the included RCTs enrolled non-pregnant adults. The GDG had no reason to think that children with COVID-19 would respond any differently to treatment with convalescent plasma. However, the risk of hospitalization in children is generally extremely low and the GDG inferred that in the absence of immunosuppression or another significant risk factor children should not receive the intervention.

For patients with severe or critical COVID-19 we recommend not to use convalescent plasma for treatment of COVID-19, except in the context of a clinical trial (recommended only in research settings).

Lopinavir-ritonavir (published 17 December 2020)

For patients with COVID-19, regardless of disease severity we recommend not to use lopinavir-ritonavir (strong recommendation against).

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

None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with lopinavir-ritonavir. There were similar considerations in

regards to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. In patients using lopinavir-ritonavir for HIV infection, it should generally be continued while receiving care for COVID-19.

Hydroxychloroquine (published 17 December 2020)

For patients with COVID-19, regardless of disease severity we recommend not to use hydroxychloroquine or chloroquine (strong recommendation against).

This recommendation applies to patients with any disease severity and any duration of symptoms. Hinweis: **None of the included RCTs enrolled children, and therefore the applicability of this recommendation to children is currently uncertain**. However, the panel had no reason to think that children with COVID-19 would respond any differently to treatment with hydroxychloroquine. There were similar considerations in regards to pregnant individuals, with no data directly examining this population, but no rationale to suggest they would respond differently than other adults. Hydroxychloroquine crosses the placental barrier and there are concerns that it may lead to retinal damage in neonates. Although hydroxychloroquine has been used in pregnant individuals with systemic autoimmune diseases, such as systemic lupus erythematosus, pregnant individuals may have even more reasons than other patients to be reluctant to use hydroxychloroquine for COVID-19.

Casirivimab-imdevimab (updated 13 January 2023)

For all patients with COVID-19, regardless of disease severity we recommend against treatment with casirivimab-imdevimab (strong recommendation against).

The GDG considered in vitro data demonstrating that casirivimab-imdevimab does not neutralize the currently circulating variants of SARS-CoV-2 and their subvariants. There was consensus among the panel that the meaningful reduction of in vitro neutralization activity strongly suggests absence of clinical effectiveness of monoclonal antibodies such as sotrovimab and casirivimab-imdevimab. There was also consensus regarding the need for clinical trial evidence in order to confirm clinical effectiveness of new monoclonal antibodies that reliably neutralize circulating strains in vitro.

In light of the recent in vitro evidence, the GDG concluded that the clinical effects of casirivimab-imdevimab for COVID-19 caused by the currently circulating variants and subvariants of SARS-CoV-2 are highly uncertain. Trials performed before these variants occurred provided overall moderate certainty evidence for modest benefits and negligible harms, as demonstrated in GRADE Summary of Findings tables available in previous versions of this living guideline.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 03 of 12, March 2025) am 03.03.2025

#	Suchschritt
1	[mh ^"COVID-19"] OR [mh "COVID-19 drug treatment"] OR [mh ^"SARS-CoV-2"] OR [mh ^"Severe Acute Respiratory Syndrome"] OR [mh "COVID-19 serotherapy"]
2	(Covid* OR 2019ncov OR cov2 OR ncov19 OR sarscov* OR (ncov* NEAR/3 2019) OR (ncov* NEAR/3 19)):ti,ab,kw
3	(coronavir* OR (corona NEXT vir*) OR betacoronavir* OR (beta NEXT coronavir*) OR SARS*):ti,ab,kw
4	((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis)):ti,ab,kw
5	("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
6	{OR #1-#5}
7	#6 with Cochrane Library publication date from Mar 2020 to Feb 2023
8	#6 with Cochrane Library publication date from Mar 2023 to present

Leitlinien und systematische Reviews in PubMed am 07.03.2025

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

verwendeter Suchfilter für systematische Reviews ohne Änderung:
Konsentierter Standardfilter für Systematische Reviews (SR), Team Informationsmanagement der Abteilung Fachberatung Medizin, Gemeinsamer Bundesausschuss, letzte Aktualisierung am 15.01.2025.

#	Suchschritt
	Leitlinien
1	COVID-19[mj] OR COVID-19 Drug Treatment[mh] OR COVID-19 serotherapy[mh] OR SARS-CoV-2[mj]
2	COVID19[ti] OR COVID-19[ti] OR "SARS-CoV-2"[ti] OR "SARSCoV2"[ti] OR "SARSCoV-2"[ti] OR "SARS-CoV2"[ti]
3	2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR (ncov*[ti] AND 2019[ti]) OR (ncov*[ti] AND 19[ti])
4	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti]
5	(#2 OR #3 OR #4) NOT medline[sb]
6	#1 OR #5

#	Suchschritt
7	(#6) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[ti] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
8	((((#7) AND ("2020/03/01"[PDAT] : "3000"[PDAT])) NOT (animals[MeSH:noexp] NOT (Humans[MesH] AND animals[MeSH:noexp])) NOT ("The Cochrane database of systematic reviews"[Journal]) NOT ((comment[ptyp]) OR letter[ptyp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
All	(((((("COVID-19"[MeSH Major Topic] OR "covid 19 drug treatment"[MeSH Terms] OR "covid 19 serotherapy"[MeSH Terms] OR "SARS-CoV-2"[MeSH Major Topic] OR (("COVID19"[Title] OR "COVID-19"[Title] OR "SARS-CoV-2"[Title] OR "SARSCoV2"[Title] OR "SARSCoV-2"[Title] OR "SARS-CoV2"[All Fields] OR ("2019ncov"[Title] OR "cov2"[Title] OR "ncov19"[Title] OR ("ncov*"[Title] AND "2019"[Title]) OR ("ncov*"[Title] AND "19"[Title])) OR ("coronavir*"[Title] OR "corona vir*"[Title] OR "betacoronavir*"[Title] OR "beta coronavir*"[Title])) NOT "medlinestatus medline"[All Fields])) AND ("Guideline"[Publication Type] OR "practice guideline"[Publication Type] OR "guideline*"[Title] OR "consensus development conference"[Publication Type] OR "consensus development conference, nih"[Publication Type] OR "recommendation*"[Title]) AND 2020/03/01:3000/12/31[Date - Publication]) NOT ("animals"[MeSH Terms:noexp] NOT ("humans"[MeSH Terms] AND "animals"[MeSH Terms:noexp]))) NOT "The Cochrane database of systematic reviews"[Journal]) NOT ("comment"[Publication Type] OR "letter"[Publication Type])) NOT ("retracted publication"[Publication Type] OR "retraction notice"[Publication Type] OR "retraction of publication"[Publication Type] OR "preprint"[Publication Type])
	systematische Reviews
9	COVID-19/therapy[mj] OR COVID-19 Drug Treatment[mh] OR COVID-19 serotherapy[mh]
10	COVID-19[mj] OR SARS-CoV-2[mj]
11	#2 OR #3 OR #4 OR #10
12	(#11) 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] OR serotherap*[ti])
13	(#9 OR #12) AND ("systematic review"[pt] OR "meta-analysis"[pt] OR "network meta-analysis"[mh] OR "network meta-analysis"[pt] OR (systematic*[tiab] AND (review*[tiab] OR overview*[tiab])) OR metareview*[tiab] OR umbrella review*[tiab] OR "overview of reviews"[tiab] OR meta-analy*[tiab] OR metaanaly*[tiab] OR metanaly*[tiab] OR meta-synthes*[tiab] OR metasynthes*[tiab] OR meta-study[tiab] OR metastudy[tiab] OR integrative review[tiab] OR integrative literature review[tiab] OR evidence review[tiab] OR (("evidence-based medicine"[mh] OR evidence synthes*[tiab]) AND "review"[pt]) OR ((("evidence based"[tiab:~3]) OR evidence base[tiab]) AND (review*[tiab] OR overview*[tiab])) OR (review[ti] AND (comprehensive[ti] OR studies[ti] OR trials[ti])) OR ((critical appraisal*[tiab] OR critically appraise*[tiab] OR study selection[tiab] OR

#	Suchschritt
	((predetermined[tiab] OR inclusion[tiab] OR selection[tiab] OR eligibility[tiab]) AND criteri*[tiab]) OR exclusion criteri*[tiab] OR screening criteri*[tiab] OR systematic*[tiab] OR data extraction*[tiab] OR data synthes*[tiab] OR prisma*[tiab] OR moose[tiab] OR entreq[tiab] OR mecir[tiab] OR stard[tiab] OR strobe[tiab] OR "risk of bias"[tiab]) AND (survey*[tiab] OR overview*[tiab] OR review*[tiab] OR search*[tiab] OR analysis[ti] OR apprais*[tiab] OR research*[tiab] OR synthes*[tiab]) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR bibliographies[tiab] OR published[tiab] OR citations[tiab] OR database*[tiab] OR references[tiab] OR reference-list*[tiab] OR papers[tiab] OR trials[tiab] OR studies[tiab] OR medline[tiab] OR embase[tiab] OR cochrane[tiab] OR pubmed[tiab] OR "web of science" [tiab] OR cinahl[tiab] OR cinhal[tiab] OR scisearch[tiab] OR ovid[tiab] OR ebsco[tiab] OR scopus[tiab] OR epistemonikos[tiab] OR prospero[tiab] OR proquest[tiab] OR lilacs[tiab] OR biosis[tiab])) OR "technical report"[pt] OR HTA[tiab] OR technology assessment*[tiab] OR technology report*[tiab])
14	(((#13) AND ("2020/03/01"[PDAT] : "3000"[PDAT]) NOT "The Cochrane database of systematic reviews"[Journal]) NOT (animals[MeSH:noexp] NOT (Humans[mh] AND animals[MeSH:noexp]))) NOT ("retracted publication"[pt] OR "retraction notice"[pt] OR "retraction of publication"[pt] OR "preprint"[pt])
	systematische Reviews ohne Leitlinien
15	(#14) NOT (#8)
16	(#15) AND ("2023/03/01"[PDAT] : "3000"[PDAT])
17	#15 NOT #16

Iterative Handsuche nach grauer Literatur, abgeschlossen am 07.03.2025

- Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF)
- National Institute for Health and Care Excellence (NICE)
- Scottish Intercollegiate Guideline Network (SIGN)
- World Health Organization (WHO)
- ECRI Guidelines Trust (ECRI)
- Dynamed / EBSCO
- Guidelines International Network (GIN)
- Trip Medical Database

Referenzen

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2. **Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN), Deutsche Interdisziplinäre Vereinigung für Intensiv- und Notfallmedizin (DIVI), Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin (DGP), Deutsche Gesellschaft für Infektiologie (DGI).** Empfehlungen zur Therapie von Patienten mit COVID-19: Living guideline; S3-Leitlinie, Vers. 11 [online]. AWMF-Registernummer 113-001. 02.2025. Berlin (GER): Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF); 2024. [Zugriff: 26.05.2025]. URL: https://register.awmf.org/assets/guidelines/113-001l_S3_Empfehlungen-zur-Therapie-von-Patienten-mit-COVID-19_2025-04.pdf.

3. **Infectious Diseases Society of America (IDSA).** Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: vers. 11 [online]. 12.08.2024. Arlington (USA): IDSA; 2023. [Zugriff: 26.05.2025]. URL: https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v11.0.0.pdf.

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

Gemeinsamer Bundesausschuss

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

- keine eingegangenen schriftlichen Rückmeldungen gem. § 7 Absatz 6 VerfO