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: 2022-B-245-z Remdesivir

Stand: Oktober 2022

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

Remdesivir
Behandlung von Kindern und Jugendlichen (ab 4 Wochen und unter 18 Jahren) mit COVID-19

Kriterien gemäß 5. Kapitel § 6 VerfO	
Sofern als Vergleichstherapie eine Arzneimittelanwendung in Betracht kommt, muss das Arzneimittel grundsätzlich eine Zulassung für das Anwendungsgebiet haben.	*Siehe Übersicht „II. Zugelassene Arzneimittel im Anwendungsgebiet“*
Sofern als Vergleichstherapie eine nicht-medikamentöse Behandlung in Betracht kommt, muss diese im Rahmen der GKV erbringbar sein.	nicht angezeigt
Beschlüsse/Bewertungen/Empfehlungen des Gemeinsamen Bundesausschusses zu im Anwendungsgebiet zugelassenen Arzneimitteln/nicht-medikamentösen Behandlungen	- Casirivimab/Imdevimab (Jugendliche ab 12 Jahre und Erwachsene, ohne zusätzliche Sauerstoff-therapie und mit erhöhtem Risiko für einen schweren Verlauf), Beschluss über die Nutzenbewertung nach§ 35a SGB V vom 06. Oktober 2022. - Remdesivir (Jugendliche ab 12 Jahre und Erwachsene, mit zusätzlicher Sauerstoffzufuhr), Beschluss über die Nutzenbewertung nach§ 35a SGB V vom 16. September 2021.
Die Vergleichstherapie soll nach dem allgemein anerkannten Stand der medizinischen Erkenntnisse zur zweckmäßigen Therapie im Anwendungsgebiet gehören.	*Siehe systematische Literaturrecherche*

II. Zugelassene Arzneimittel im Anwendungsgebiet

Wirkstoff **ATC-Code** **Handelsname**	**Anwendungsgebiet**
Zu bewertendes Arzneimittel:	
Remdesivir J05AB16 Veklury®	Veklury wird angewendet zur Behandlung der Coronavirus-Krankheit 2019 (COVID-19) bei: • Erwachsenen und pädiatrischen Patienten (im Alter von mindestens 4 Wochen und mit einem Körpergewicht von mindestens 3 kg) mit einer Pneumonie, die eine zusätzliche Sauerstoffzufuhr erfordert (Low- oder High-Flow Sauerstofftherapie oder eine andere nicht-invasive Beatmung zu Therapiebeginn) • Erwachsenen und pädiatrischen Patienten (mit einem Körpergewicht von mindestens 40 kg), die keine zusätzliche Sauerstoffzufuhr benötigen und ein erhöhtes Risiko haben, einen schweren COVID-19-Verlauf zu entwickeln.
Dexamethason H02AB02 Dexa inject JENAPHARM®	Dexa 4/8/40/100 mg inject JENAPHARM wird angewendet zur Behandlung der Coronavirus-Krankheit 2019 (COVID-19) bei Erwachsenen und Jugendlichen (im Alter von mindestens 12 Jahren und mit einem Körpergewicht von mindestens 40 kg), die eine zusätzliche Sauerstoffzufuhr erfordert.
Casirivimab/ Imdevimab N/N Ronapreve®	Ronapreve wird angewendet zur: - Behandlung einer Coronavirus-2019-Erkrankung (COVID-19) bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht, die keine zusätzliche Sauerstofftherapie benötigen und bei denen ein erhöhtes Risiko für einen schweren Verlauf von COVID-19 besteht. - Prophylaxe von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren mit mindestens 40 kg Körpergewicht. Bei der Anwendung von Ronapreve sind Informationen über die Aktivität von Ronapreve gegen besorgniserregende Virusvarianten zu berücksichtigen.
Sotrovimab N/N Xevudy®	Xevudy ist zur Behandlung von Erwachsenen und Jugendlichen (ab 12 Jahren und mit einem Körpergewicht von mindestens 40 kg) mit einer Coronavirus-Krankheit-2019 (coronavirus disease 2019, COVID-19) indiziert, die keine Sauerstoff-Supplementierung benötigen und ein erhöhtes Risiko für einen schweren Krankheitsverlauf von COVID-19 haben.

II. Zugelassene Arzneimittel im Anwendungsgebiet	
Tixagevimab / Cilgavimab J06BD03 Evusheld®	EVUSHELD wird angewendet zur Behandlung einer Coronavirus-19-Erkrankung bei Erwachsenen und Jugendlichen (ab 12 Jahren mit mindestens 40 kg Körpergewicht), die keine zusätzliche Sauerstoffzufuhr benötigen und bei denen ein erhöhtes Risiko für einen schweren Verlauf von COVID-19 besteht

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2022-B-245(Remdesivir)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	11. Oktober 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
ECMO	extracorporeal mechanical oxygenation
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development, and Evaluation
IDSA	Infectious Diseases Society of America
KI	Konfidenzintervall
LoE	Level of Evidence
mAB	monoklonaler Antikörper
MAGICapp	Making GRADE the Irresistible Choice
MERS	Middle East Respiratory Syndrome
nCOV-2019	novel Coronavirus-2019
NICE	National Institute for Health and Care Excellence
NIH	National Institute of Health
OR	Odds Ratio
RCT	Randomized Controlled Trial
ROBINS	Risk of Bias Instrument for Non-randomized Studies - of Interventions
RR	Relatives Risiko
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
SpO_2	percentage of oxyhemoglobin saturation
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Behandlung von Kindern und Jugendlichen ab 4 Wochen und unter 18 Jahren mit COVID-19

Hinweis zur Synopse: Informationen hinsichtlich nicht zugelassener Therapieoptionen sind über die vollumfängliche Darstellung der Leitlinienempfehlungen dargestellt.

2 Systematische Recherche

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

Der Suchzeitraum wurde auf die letzten fünf Jahre eingeschränkt und die Recherche am 06.10.2022 abgeschlossen. Die detaillierte Darstellung der Recherchestrategie inkl. verwendeter Suchfilter sowie eine Angabe durchsuchter Leitlinienorganisationen ist am Ende der Synopse aufgeführt. Mit Hilfe von EndNote wurden Dubletten identifiziert und entfernt. Die Recherche ergab 905 Referenzen.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Referenzen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 6 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnte kein CR identifiziert werden.

3.2 Systematische Reviews

Es konnte kein Systematischer Review identifiziert werden.

3.3 Leitlinien

Fraile Navarro D et al., 2022 [1].

Clinical care of children and adolescents with COVID-19: recommendations from the National COVID-19 Clinical Evidence Taskforce

Zielsetzung/Fragestellung

To develop recommendations specific to paediatric COVID-19 care

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium; Eltern von betroffenen Patienten werden einbezogen
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt; trifft zu
- Systematische Suche, Auswahl und Bewertung der Evidenz; trifft teilweise 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 teilweise zu
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- „Living Systematic Review“

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; unclear balance 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.
- Wenn klinische Studien keine Kinder und / oder Jugendliche einschlossen, wurde automatisch eine Stufe nach unten bewertet

Sonstige methodische Hinweise

- Safety und Pharmakokinetische Daten wurden von Kindern einbezogen, während Efficacy Daten extrapoliert wurden
- Wenn keinerlei systematische klinische Evidenz verfügbar für Kinder und / oder Jugendliche wurden die Empfehlungen auf Basis von „Best practice" geschlossen

Treatments for COVID-19

Corticosteroids (GRADE: low certainty; 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 are receiving oxygen (including mechanically ventilated patients).

Dexamethasone (GRADE: low certainty; conditional recommendation)

Do not routinely use dexamethasone (or other corticosteroids) to treat COVID-19

in children or adolescents who do not require oxygen

Tocilizumab (GRADE: low certainty; 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

Corticosteroids
Evidence informing these recommendations comes from a recent meta-analysis of seven randomised controlled trials of patients with critical COVID-19; one study of patients with moderate, severe and critical COVID-19; and one study of patients with severe COVID-19.[36] Evidence indicates that corticosteroids reduce deaths in adult patients with critical or severe COVID-19, but may increase deaths in adult patients with moderate COVID-19. Although these trials did not include children, due to a reduction in death along with no important resource implications and the likely acceptability of these drugs, we recommend considering using corticosteroids in children and adolescents with COVID-19 who are receiving oxygen, including mechanically ventilated children.

Tocilizumab
The evidence supporting the use of tocilizumab comes from tenrandomised trials that compared tocilizumab with standard care in 6570 adults hospitalised with COVID-19. The majority of data are from the RECOVERY trial, which included 4116 adults hospitalised with moderate to critical COVID-19.26 Evidence indicates that tocilizumab probably reduces the risk of death in hospitalised adults who require supplemental oxygen, as well as reducing the need for invasive mechanical ventilation and admission to the intensive care unit. Given this evidence, the previous experience on using tocilizumab in children plus the absence of trials in children and adolescents, the PAC Panel formulated a conditional recommendation supporting the use of tocilizumab in children and adolescents.

Infectious Diseases Society of America (IDSA), 2022 [2].

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 10.0.0

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Ovid Medline and Embase were searched through May 31, 2022
- Letzte Aktualisierung: August 30, 2022

LoE/GoR

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

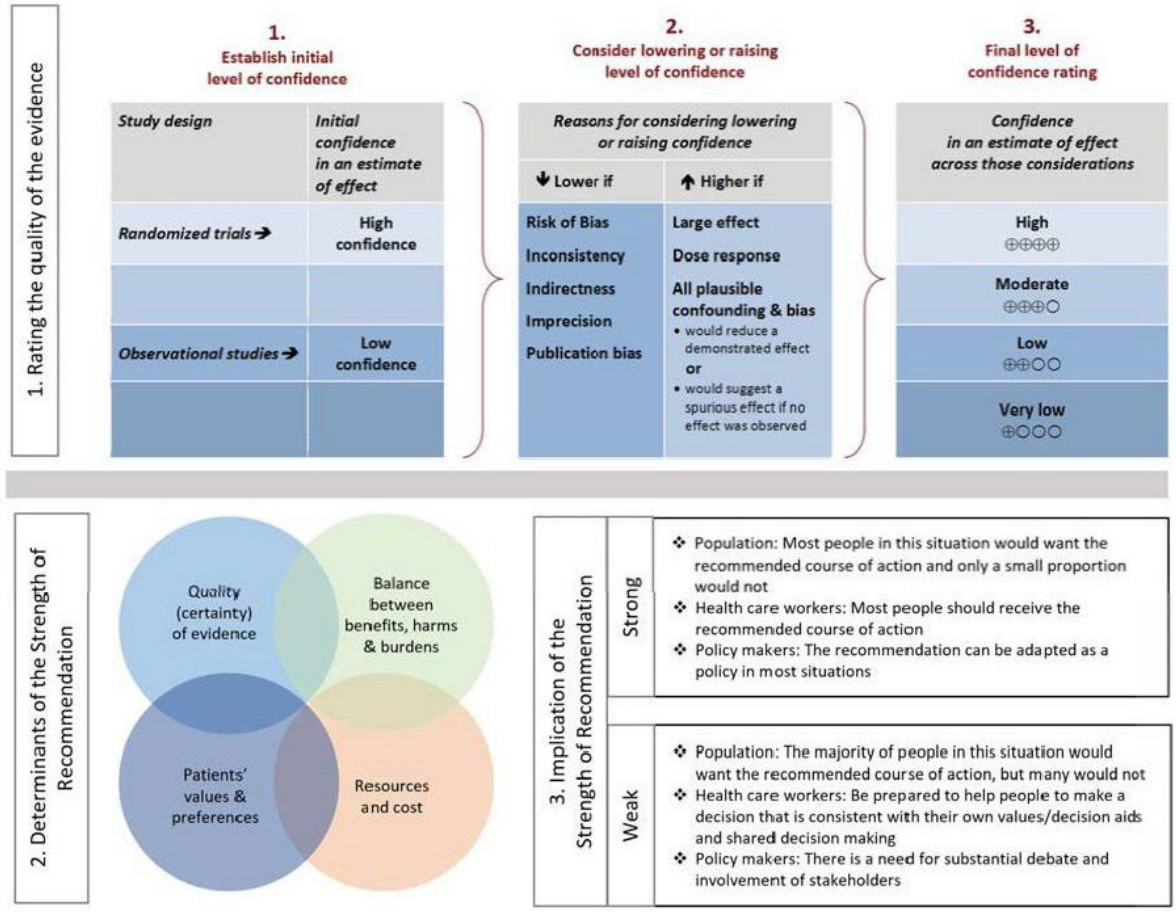

Abbildung 1: Approach and implications to rating the quality of evidence and strength of recommendations using the GRADE methodology (unrestricted use of the figure granted by the U.S. GRADE Network)

Sonstige methodische Hinweise

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

Empfehlungen

Corticosteroids

Section last reviewed and updated 9/25/2020

Last literature search conducted 9/4/2020

- Recommendation 7: Among hospitalized critically ill patients* with COVID-19, the IDSA guideline panel recommends dexamethasone rather than no dexamethasone. (Strong recommendation, Moderate certainty of evidence)
  - Remark: If dexamethasone is unavailable, equivalent total daily doses of alternative glucocorticoids may be used. Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
  - Severity definition: *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.
- Recommendation 8: Among hospitalized patients with severe*, but non-critical, COVID-19 the IDSA guideline panel suggests dexamethasone rather than no dexamethasone. (Conditional recommendation, Moderate certainty of evidence)
  - Remark: Dexamethasone 6 mg IV or PO for 10 days (or until discharge) or equivalent glucocorticoid dose may be substituted if dexamethasone unavailable. Equivalent total daily doses of alternative glucocorticoids to dexamethasone 6 mg daily are methylprednisolone 32 mg and prednisone 40 mg.
  - Severity definition: *Severe illness is defined as patients with SpO2 ≤94% on room air, including patients on supplemental oxygen.
- Recommendation 9: Among hospitalized patients with non-severe* COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids. (Conditional recommendation, Low certainty of evidence)
  - Severity definition: *Non-severe illness is defined as patient with a SpO2 > 94%not requiring supplemental oxygen.

<u>Inhaled Corticosteroids</u>

Section last reviewed and updated 3/14/2022

Last literature search conducted 2/28/2022

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

<u>IL-6 blockade</u>

Section last reviewed and updated 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.
  - Severity definitions:

- *Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.
- **Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

Neutralizing Antibodies for Treatment

Section last reviewed and updated 5/23/2022

Last literature search conducted 4/30/2022

- Recommendation 21: In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests post-exposure casirivimab/imdevimab only when predominant regional variants* are susceptible to the agent**. (Conditional recommendation†, Low certainty of evidence)
  - *Severe illness is defined as patients with SpO_2 ≤94% on room air, including patients on supplemental oxygen.
  - **Critical illness is defined as patients on mechanical ventilation and ECMO. Critical illness includes end organ dysfunction as is seen in sepsis/septic shock. In COVID-19, the most commonly reported form of end organ dysfunction is ARDS.

†*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.*

National COVID-19 Clinical Evidence Taskforce, 2022 [4].

Australian guidelines for the clinical care of people with COVID-19: version 65.1

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Ständige Aktualisierung: 28.09.2022

LoE/GoR

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

6.1 Recommended disease-modifying treatments

6.1.1 Casirivimab plus imdevimab (Ronapreve)

6.1.1.3 Casirivimab plus imdevimab (Ronapreve) for children and adolescents

Consensus recommendation

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

Only in research settings

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

Consensus recommendation

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

Not recommended

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

6.1.2 Corticosteroids (inhaled)

6.1.2.2 Corticosteroids (inhaled) for children and adolescents

Conditional recommendation

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

6.1.3 Corticosteroids (systemic)

6.1.3.3 Corticosteroids (systemic) for children and adolescents

Conditional recommendation

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

Conditional recommendation against

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

6.1.8 Sotrovimab

6.1.8.3 Sotrovimab for children and adolescents

Info Box

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).

Consensus recommendation

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

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

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

National Institute for Health and Care Excellence (NICE), 2022 [5].

COVID-19 rapid guideline: managing COVID-19; version 27.5

Zielsetzung/Fragestellung

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

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

Methodik

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

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

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

<u>Grundlage der Leitlinie</u>

- Repräsentatives Gremium: keine Patientenvertreter;
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt;
- Systematische Suche, Auswahl und Bewertung der Evidenz:

- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt;
- Regelmäßige Überprüfung der Aktualität gesichert.

Recherche/Suchzeitraum:

- Living guidline: As there is a need for prompt guidance on therapeutics for managing COVID-19, NICE is collaborating with other guideline development teams to produce evidence reviews. NICE has reused data from the National Australian COVID-19 clinical evidence taskforce for some recommendations.
- Letzte Aktualisierung: 27.07.2022

LoE/GoR

- GRADE

EMPFEHLUNGEN

7.2 Neutralising monoclonal antibodies - for people not in hospital

Recommended

Offer a neutralising monoclonal antibody for people aged 12 and over with COVID-19 who:

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

7.3 Corticosteroids

Recommended

Offer dexamethasone, or either hydrocortisone or prednisolone when dexamethasone cannot be used or is unavailable, to people with COVID-19 who:

- need supplemental oxygen to meet their prescribed oxygen saturation levels or
- have a level of hypoxia that needs supplemental oxygen but who are unable to have or tolerate it.

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

Use of corticosteroids in children was considered. The panel decided that the recommendation should not be limited to adults because the evidence included both adults and children. The panel therefore agreed to avoid age-specific wording in the recommendation. Instead, they agreed that the dosing for adults and children should be provided as supplementary advice. Paediatric experts highlighted that the risk of progression for a child with a stable minimal oxygen requirement is not as high as for adults. Therefore, they suggested cross reference to Royal College of Child and Paediatric Health risk criteria markers for assessing corticosteroid use. For preterm babies with a corrected gestational age of less than 44 weeks, specialist advice is considered necessary because evidence is lacking for corticosteroid use in this age group.

Not recommended

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.

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

Not recommended

New

Do not offer a combination of casirivimab and imdevimab to people hospitalised because of COVID-19 who are known or suspected to have infection caused by an Omicron variant (or any other variant not susceptible to casirivimab and imdevimab).

In vitro data suggests that Omicron, the current dominant variant in England, is not susceptible to the combination of casirivimab and imdevimab.

As of 24 February 2022, NHS England has removed casirivimab and imdevimab from their Interim Clinical Commissioning Policy and there is currently no access to this treatment in England. For information on medicines that can be accessed for people in hospital because of COVID-19 see the NHS England Rapid Clinical Policy development: COVID-19 page.

Conditional recommendation

Only offer a combination of casirivimab and imdevimab to people aged 12 and over hospitalised because of COVID-19 when:

- the infection is known to be caused by a variant susceptible to casirivimab and imdevimab, and
- the person has no detectable SARS-CoV-2 antibodies (seronegative).

WHO, 2022 [6].

Therapeutics and COVID-19: living guideline; WHO-2019-nCoV-therapeutics-2022.3

Zielsetzung/Fragestellung

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

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- Living systematic review. Letzte Aktualisierung: 14.07.2022

LoE/GoR

- GRADE methodology

Empfehlungen

6.4 Sotrovimab (updated 16 September 2022)

For patients with non-severe COVID-19

Strong recommendation against — Updated

We recommend against treatment with sotrovimab *(strong recommendation against)*.

6.5 Casirivimab-imdevimab (updated 16 September 2022)

For all patients with COVID-19

Strong recommendation against — Updated

We recommend against treatment with casirivimab-imdevimab *(strong recommendation against)*.

6.13 Systemic corticosteroids (published 2 September 2020)

For patients with severe or critical COVID-19

Strong recommendation for

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.

The recommendation does not apply to the following uses of corticosteroids: transdermal or inhaled administration, high-dose or long-term regimens, or prophylaxis.

For patients with non-severe COVID-19 infection

Conditional recommendation against

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

Liu E et al., 2020 [3].

Rapid advice guidelines for management of children with COVID-19

Zielsetzung/Fragestellung

This guideline focuses on the management of children younger than 18 years old infected with SARS-CoV-2, including screening, diagnosis, treatment, and patient education.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- A search strategy will be developed and implemented to identify literature published since 2003 [considering the first novel coronavirus caused the severe acute respiratory syndrome (SARS) outbreak was in 2003] to February 2020.
- The following databases will be searched: PubMed, EMBASE, Cochrane library, Web of Science, WANFANG, CNKI, and CBM.
- There will be no restriction on publication type

LoE/GoR

Table 1 Grading of quality of evidence and strength of recommendations

Quality of evidence	Description
High quality of evidence	We are very confident that the true effect lies close to that of the estimate of the effect
Moderate quality of evidence	We are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
Low quality of evidence	Our confidence in the effect estimate is limited: the true effect maybe substantially different from the estimate of the effect
Very low quality of evidence	We have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect
Strength of recommendation	Description
Strong	Advantages of intervention significantly outweigh disadvantages or disadvantages of intervention significantly outweigh advantages
Weak	Advantages of intervention may outweigh disadvantages or disadvantages of intervention may outweigh advantages or the relationship between advantages and disadvantages is not clear

Sonstige methodische Hinweise

- The guideline has been registered at the International Practice Guidelines Registry Platform (registration No. IPGRP-2020CN008), and the protocol of the guideline has been published (19). This guideline was developed in accordance with the WHO handbook for guideline development, and the drafting and reporting of the full text followed the RIGHT (Reporting Items for Practice Guidelines in Healthcare) statement (20,21).

Empfehlungen

Clinical question 4: should antiviral drugs such as ribavirin, interferon, remdesivir (GS-5734), lopinavir/ritonavir or oseltamivir be used to treat children with COVID-19?

Recommendation 4: antiviral drugs to treat COVID-19 in children should only be used in the context of clinical trials (strong recommendation, low quality of evidence)

- Rationale: Most viral diseases are self-limiting illnesses that do not require specific antiviral therapy. Several guidelines recommend antiviral drugs such as

lopinavir/ritonavir (LPV/r), interferon, arbidol and hydroxychloroquine to treat COVID-19 (36,40,41). In China, almost all children with COVID-19 received antiviral therapy (42). However, there is no evidence of the effectiveness of antiviral therapy in children with COVID-19. Published studies have shown that LPV/r and arbidol are not effective against COVID-19, and the efficacy of remdesivir is still controversial (43,44).

- Evidence summary: A rapid review included 23 studies (six randomized controlled trials and 17 cohort studies) with 6,008 patients. None of the studies included direct evidence in children with COVID-19. In adults with COVID-19, the use of LPV/r had no effect on mortality [relative risk (RR) = 0.77, 95% CI: 0.45 to 1.30] and probability of negative a PCR test (RR =0.98, 95% CI: 0.82 to 1.18). Arbidol had no benefit on the probability of a negative PCR test (RR =1.27, 95% CI: 0.93 to 1.73). Hydroxychloroquine was effective for promoting the remission of radiographic abnormalities (RR =1.47, 95% CI: 1.02 to 2.11) and decreasing the duration of fever [weighted mean difference (WMD) =−0.90 days, 95% CI: −1.48 to −0.31], but it was not associated with the probability of a negative PCR result (RR =0.93, 95% CI: 0.73 to 1.18). There was also no statistically significant difference in the incidence of adverse reactions between the patients receiving the above antiviral drugs and the respective control groups (45).

Clinical question 6: should systemic corticosteroids be used to treat children with severe COVID-19?

Recommendation 6: systemic glucocorticoids should not be used routinely for children with COVID-19 (strong recommendation, low quality of evidence). Only low-dose and short-duration systemic glucocorticoid therapy can be used for children with severe COVID-19 in the context of clinical trials (weak recommendation, very low quality of evidence)

- Rationale: Systemic glucocorticoids are highly effective anti-inflammatory drugs, but their use in severe respiratory viral infections remains controversial. Evidence has shown that systemic glucocorticoids may have no benefit in severe cases of COVID-19, SARS and MERS, and severe side effects such as femoral head necrosis may occur after high dose administrations.
- Evidence summary: A rapid review included 23 studies (one RCT, 22 cohort studies) with 13,815 patients. There was no direct evidence from children with COVID-19. In adults with COVID-19, the use of systemic glucocorticoids did not reduce mortality (RR =2.00, 95% CI: 0.69 to 5.75) or the duration of lung inflammation (WMD =−1 day, 95% CI: −2.91 to 0.91). In patients with SARS, glucocorticoids also did not reduce the mortality (RR =1.52, 95% CI: 0.89 to 2.60), duration of fever (WMD =0.82 days, 95% CI: −2.88 to 4.52) or duration of lung inflammation absorption (WMD =0.95 days, 95% CI: −7.57 to 9.48). The use of systemic glucocorticoid therapy prolonged the duration of hospital stay in patients with COVID-19 (WMD =2.43 days, 95% CI: 1.42 to 3.43), SARS (WMD =6.83 days, 95% CI: 1.48 to 12.17) and MERS (WMD =6.30 days, 95% CI: 2.36 to 10.24). Long-term use of high-dose glucocorticoids increased the risk of adverse reactions in patients with SARS such as coinfections (RR =3.52, 95% CI: 2.33 to 5.32) (47).

Referenzen

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20. WHO. WHO handbook for guideline development. 2014. Available online: https://apps.who.int/medicinedocs/en/m/abstract/Js22083en/ (accessed March 16, 2020).
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47. Lu S, Zhou Q, Hang L, et al. Effectiveness and safety of glucocorticoids to treat COVID-19: a rapid review and meta-analysis. Ann Transl Med 2020;8:627.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 9 of 12, September 2022) am 23.09.2022

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

Systematic Reviews in PubMed am 23.09.2022

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

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

#	Suchfrage
8	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8
10	(#9) AND (treatment*[ti] OR treating[ti] OR treated[ti] OR treat[ti] OR treats[ti] OR treatab*[ti] OR therapy[ti] OR therapies[ti] OR therapeutic*[ti] OR monotherap*[ti] OR polytherap*[ti] OR pharmacotherap*[ti] OR effect*[ti] OR efficacy[ti] OR management[ti] OR drug*[ti] OR intervent*[ti] OR (standard*[ti] AND care[ti]) OR antiviral*[ti] OR anti-viral*[ti] OR "Antiviral Agents"[mj] OR immunotherap*[ti] OR Immunotherapy[mj])
11	#1 OR #2 OR #10
12	adolesc*[tiab] OR babies[tiab] OR baby*[tiab] OR boy[tiab] OR boyhood*[tiab] OR boys[tiab] OR child*[tiab] OR girl[tiab] OR girlhood*[tiab] OR girls[tiab] OR infan*[tiab] OR juvenile*[tiab] OR kid[tiab] OR kids[tiab] OR minors*[tiab] OR neonat*[tiab] OR new-born[tiab] OR newborn*[tiab] OR NICU[tiab] OR NICUs[tiab] OR paediat*[tiab] OR pediat*[tiab] OR perinat*[tiab] OR PICU[tiab] OR PICUs[tiab] OR postmatur*[tiab] OR postmenarch*[tiab] OR post menarch*[tiab] OR postnat*[tiab] OR postneonat*[tiab] OR preadolesc*[tiab] OR premenarch*[tiab] OR pre menarch*[tiab] OR prematur*[tiab] OR prepuberty*[tiab] OR prepubescen*[tiab] OR preschool*[tiab] OR preterm*[tiab] OR puberty[tiab] OR pubescen*[tiab] OR teen*[tiab] OR toddler*[tiab] OR under-age[tiab] OR under-aged[tiab] OR underag*[tiab] OR young*[tiab] OR youth*[tiab] OR adolescent[mh] OR child[mh] OR infant[mh] OR young adult[mh] OR puberty[mh] OR pediatrics[mh]
13	#11 AND #12
12	(#13) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR

#	Suchfrage
	bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
13	(#14) AND ("2017/09/01"[PDAT] : "3000"[PDAT])
14	(#15) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in PubMed am 23.09.2022

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

#	Suchfrage
1	COVID-19/therapy[MeSH Terms]
2	COVID-19 drug treatment[Supplementary Concept] OR Coronavirus Infections/drug therapy[mh:noexp] OR Coronavirus Infections/therapy[mh:noexp]
3	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
4	Covid*[ti] OR 2019ncov[ti] OR cov2[ti] OR ncov19[ti] OR sarscov*[ti] OR (ncov[ti] AND 2019[ti]) OR (ncov[ti] AND 19[ti])
5	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
6	(cov[ti]) AND (novel[ti] OR new[ti] OR 2019[ti] OR 19[ti] OR infection*[ti] OR disease*[ti] OR wuhan[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
8	(("Severe Acute Respiratory Syndrome"[ti] OR "Severe Acute Respiratory Syndromes"[ti] OR "sudden acute respiratory syndrome"[ti]) AND "2"[ti]) OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
9	#3 OR #4 OR #5 OR #6 OR #7 OR #8

#	Suchfrage
10	(#9) AND (treatment*[ti] OR treating[ti] OR treated[ti] OR treat[ti] OR treats[ti] OR treatab*[ti] OR therapy[ti] OR therapies[ti] OR therapeutic*[ti] OR monotherap*[ti] OR polytherap*[ti] OR pharmacotherap*[ti] OR effect*[ti] OR efficacy[ti] OR management[ti] OR drug*[ti] OR intervent*[ti] OR (standard*[ti] AND care[ti]) OR antiviral*[ti] OR anti-viral*[ti] OR "Antiviral Agents"[mj] OR immunotherap*[ti] OR Immunotherapy[mj])
11	#1 OR #2 OR #10
12	adolesc*[tiab] OR babies[tiab] OR baby*[tiab] OR boy[tiab] OR boyhood*[tiab] OR boys[tiab] OR child*[tiab] OR girl[tiab] OR girlhood*[tiab] OR girls[tiab] OR infan*[tiab] OR juvenile*[tiab] OR kid[tiab] OR kids[tiab] OR minors*[tiab] OR neonat*[tiab] OR new-born[tiab] OR newborn*[tiab] OR NICU[tiab] OR NICUs[tiab] OR paediat*[tiab] OR pediat*[tiab] OR perinat*[tiab] OR PICU[tiab] OR PICUs[tiab] OR postmatur*[tiab] OR postmenarch*[tiab] OR post menarch*[tiab] OR postnat*[tiab] OR postneonat*[tiab] OR preadolesc*[tiab] OR premenarch*[tiab] OR pre menarch*[tiab] OR prematur*[tiab] OR prepuberty*[tiab] OR prepubescen*[tiab] OR preschool*[tiab] OR preterm*[tiab] OR puberty[tiab] OR pubescen*[tiab] OR teen*[tiab] OR toddler*[tiab] OR under-age[tiab] OR under-aged[tiab] OR underag*[tiab] OR young*[tiab] OR youth*[tiab] OR adolescent[mh] OR child[mh] OR infant[mh] OR young adult[mh] OR puberty[mh] OR pediatrics[mh]
13	#11 AND #12
14	(#13) AND ((Guideline[ptyp] OR Practice Guideline[ptyp] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]) OR ((guideline*[ti] OR recommendation*[ti]) NOT (letter[ptyp] OR comment[ptyp])))
15	(#14) AND ("2017/09/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 06.10.2022

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

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

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

Referenzen

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

[B] **McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C.** PRESS Peer Review of Electronic Search Strategies: 2015 Guideline Statement. J Clin Epidemiol 2016;75:40-46. https://doi.org/10.1016/j.jclinepi.2016.01.0

Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6
2022-B-245-z

Indikation gemäß Beratungsantrag

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). Adults and paediatric patients (weighing at least 40kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

Was ist der Behandlungsstandard in o.g. Indikation unter Berücksichtigung der vorliegenden Evidenz? Wie sieht die Versorgungspraxis in Deutschland aus?

Der aktuelle Behandlungsstandard (für Erwachsene) ist in der Living Guideline „S3-Leitlinie - Empfehlungen zur stationären Therapie von Patienten mit COVID-19“, die am 12.09.2022 aktualisiert wurde, sowie für den ambulanten hausärztlichen Bereich in der living S2e-Leitlinie, AWMF-Register-Nr. 053-054, deren erneute Aktualisierung mit der Version 23 demnächst publiziert wird, niedergeschrieben.

In der COVID-19 Frühphase können Patienten mit Risikofaktoren für einen schweren Verlauf antiviral behandelt werden, um dieses Risiko zu reduzieren. Zur Verfügung stehen aktuell Nirmatrelvir/Ritonavir (≤ 5d nach Symptombeginn), Remdesivir (≤ 7d nach Symptombeginn) und Molnupiravir (≤ 5d nach Symptombeginn). Im Falle einer Therapie erfolgt diese als Einzelfallentscheidung unter Einbeziehung von Verfügbarkeit, Kontraindikationen, Hospitalisierungsstatus und individuellem Patientenrisiko. Der Monoklonale Antikörper (MAK) Sotrovimab wird für die Therapie nicht mehr empfohlen, da er bei den derzeit in Deutschland dominierenden Omikron-Sublinien nicht ausreichend (in vitro) wirksam ist. Alle Patienten mit mindestens Low-Flow-Sauerstoff-Bedarf oder schwererem Erkrankungsverlauf sollen Dexamethason erhalten (WHO Skala 5-9). Patienten mit Low-Flow- oder High-Flow-Sauerstofftherapie (WHO Skala 5-6) können zusätzlich mit dem JAK-1 Antagonist Baricitinib behandelt werden. Ein klinischer Nutzen einer Therapie mit dem IL-6-Antagonisten Tocilizumab ist nur bei Patienten mit Sauerstoffbedarf und rasch progredientem Krankheitsverlauf hin zum respiratorischen Versagen (WHO Skala (5)/(6) zu erwarten und kann damit bei dieser Gruppe empfohlen werden.

Alle genannten Medikamente sind in Deutschland verfügbar. Zur tatsächlichen Versorgungspraxis liegen uns keine aktuellen Analysen vor.

Quelle: Living Guideline „S3-Leitlinie - Empfehlungen zur stationären Therapie von Patienten mit COVID-19“, Version 12.09.2022. https://www.awmf.org/leitlinien/detail/ll/113-001LG.html

Von Seiten der DEGAM sind bei ambulanten Patientinnen und Patienten mit SARS-CoV-2-Infektion und Risiko für

Indikation gemäß Beratungsantrag

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). Adults and paediatric patients (weighing at least 40kg) who do not require supplemental oxygen and who are at increased risk of progressing to severe COVID-19.

einen schweren Verlauf auch Budesonid-Inhalationen möglich (Off-label-Therapie, „kann"-Empfehlung, Empfehlungsgrad 0). (Quelle: SARS-CoV-2/Covid-19 - Informationen & Praxishilfen für niedergelassene Hausärztinnen und Hausärzte, S2e-Leitlinie, AWMF-Register-Nr. 053-054; https://www.awmf.org/leitlinien/detail/ll/053-054.html). Alle anderen Empfehlungen der DEGAM bezüglich der Therapie ambulanter Patientinnen und Patienten sind mit den aktualisierten Empfehlungen zur stationären Therapie (s.o.) abgestimmt und identisch – und werden in Version 23 der DEGAM-Leitlinie angepasst sein.

Die Deutsche Gesellschaft für Pädiatrische Infektiologie hat zusammen mit anderen Fachgesellschaften ein Update ihrer ersten Stellungnahme zur COVID-19 Therapie bei Kindern veröffentlicht „Stellungnahme der DGPI, API, DGKJ, DGPK, GPOH, GKJR, GPP und STAKOB zur Klinik, Diagnostik und Therapie von Kindern mit COVID-19 – Update Februar 2022". Dabei handelt es sich um einen Expertenkonsens.

https://dgpi.de/klinik-diagnostik-therapie-kinder-mit-covid-feb-2022/

Leider liegt bislang keine einzige randomisiert-kontrollierten COVID-19 Studie zu Therapien vor, die spezifisch Kinder aller Altersgruppen eingeschlossen hat. Vereinzelt gab es Studien, die Kinder über 12 Jahren eingeschlossen haben, deren Aussagekraft bzgl. des Therapienutzens bleibt jedoch aufgrund der geringer Anzahl eingeschlossener Patienten fraglich.

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von COVID-19, wenn eine zusätzliche Sauerstoffzufuhr erforderlich ist oder ein erhöhtes Risiko für einen schweren Verlauf vorliegt – insbesondere bei Kindern und Jugendlichen – die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Die Behandlung einer akuten schweren COVID-19 Infektion und eines PIMS-Syndrom wurden in der o.g. Stellungnahme ausführlich dargestellt.

Kinder mit Risikofaktoren wie schwerer Grunderkrankung haben ein erhöhtes Risiko für einen schweren Verlauf einer akuten COVID-19 Erkrankung, so dass diese Gruppe in Studien besondere Berücksichtigung finden sollte. Bei Kindern, die ein PIMS-Syndrom entwickeln, spielen Grunderkrankungen nicht so eine bedeutende Rolle. Die Daten finden sich in dem COVID-19 und PIMS-Survey auf der DGPI Homepage.

https://dgpi.de/covid-19-survey-update/

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https://dgpi.de/pims-survey-update/ Beim PIMS Syndrom liegen teils gut publizierte Studien mit akzeptablem Studiendesign vor (propensity-score-matched cohorts), allerdings fehlen auch hier klar randomisiert kontrollierte Studien. Weitere pädiatrische Studien mit solidem Studiendesign wären daher wünschenswert (gewesen).