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: 2021-B-127 Casirivimab/Imdevimab

Stand: Juli 2022

I. Zweckmäßige Vergleichstherapie: Kriterien gemäß 5. Kapitel § 6 VerfO G-BA	
Casirivimab/Imdevimab Postexpositionsprophylaxe 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	keine
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 Postexpositionsprophylaxe von COVID-19**
Zu bewertendes Arzneimittel:	
Casirivimab/ Imdevimab N/N Ronapreve®	Anwendungsgebiet laut Zulassung: - 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.
	Bisher kein zugelassenes Arzneimittel in dem relevanten Anwendungsgebiet.

Quellen: AMIce-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

Recherche und Synopse der Evidenz zur Bestimmung der zweckmäßigen Vergleichstherapie nach § 35a SGB V
Vorgang: 2021-B-127 Casirivimab/Imdevimab

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	22. Februar 2022

Inhaltsverzeichnis

Abkürzungsverzeichnis

AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CDC	Centers for Disease Control and Prevention
COVID-19	Coronavirus Disease 2019
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HCP	Health care personnel
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
PAPRs	powered air-purifying respirators
PPE	personal protective equipment
RR	Relatives Risiko
RT-PCR	Reverse-Transcription Polymerase Chain Reaction
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
TRIP	Turn Research into Practice Database
UV	ultraviolet
UVGI	UV germicidal irradiation
VHP	vaporized hydrogen peroxide
VRI	viral respiratory infection
WHO	World Health Organization

1 Indikation

Post-Expositions-Prophylaxe zur Reduktion des Risikos einer COVID-19 Infektion (laborbestätigte SARS-CoV-2-Infektion mit Symptomen) bei Erwachsenen.

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 Indikation *Prä- oder Post-Expositions-Prophylaxe einer COVID-19-Erkrankung* 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), MEDLINE (PubMed). Die Recherche nach grauer Literatur umfasste eine gezielte, iterative Handsuche auf den Internetseiten von Leitlinienorganisationen. Ergänzend wurde eine freie Internetsuche (https://www.google.com/) unter Verwendung des privaten Modus, nach aktuellen deutsch- und englischsprachigen Leitlinien durchgeführt.

Die Erstrecherche wurde am 25.06.2021 durchgeführt, die folgende am 27.01.2022. Die Recherchestrategie der Erstrecherche wurde unverändert übernommen und der Suchzeitraum jeweils auf die letzten fünf Jahre eingeschränkt. Die letzte Suchstrategie inkl. Angabe zu verwendeter Suchfilter ist am Ende der Synopse detailliert dargestellt. Die Recherchen ergaben insgesamt 1513 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 3 Referenzen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.2 Systematische Reviews

Es konnten keine relevanten Systematischen Reviews identifiziert werden.

3.3 Leitlinien

National COVID-19 Clinical Evidence Taskforce, 2022 [2].

Australian guidelines for the clinical care of people with COVID-19: version 51.0

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: 18.02.2022

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.

Recommendations

7. Chemoprophylaxis

7.1. Casirivimab plus imdevimab (REGEN-COV) for post-exposure prophylaxis

Conditional recommendation

Consider using subcutaneous casirivimab plus imdevimab as prophylaxis in seronegative or PCR-negative close household contacts of individuals with confirmed COVID-19.

The use of prophylactic casirivimab plus imdevimab probably reduces the risk of symptomatic and asymptomatic COVID-19 infection in seronegative household contacts of individuals with confirmed COVID-19 when used within 4 days of exposure. In settings for which serology testing is not readily available, consider using in unvaccinated household contacts who return a negative PCR result and who are considered unlikely to have had previous SARS-CoV-2 infection.

Results are based on one trial, in which 1200 mg of casirivimab plus imdevimab (600 mg of each) was administered subcutaneously to close household contacts of individuals with confirmed COVID-19 [571]. Participants were healthy individuals aged 12 years or older who were seronegative for SARS-CoV-2 antibodies at the time of treatment.

The following should be considered when determining the appropriateness of treatment:

- *Vaccinated individuals were excluded from the trial—the ability of casirivimab plus imdevimab to prevent COVID-19 infection in this population is not known.*
- *The effectiveness of casirivimab plus imdevimab in preventing COVID-19 infection in patients who are seropositive to SARS-CoV-2 antibodies or who are immunosuppressed is not known.*
- *In individuals who go on to develop COVID-19, the impact of prophylactic casirivimab plus imdevimab on subsequent outcomes of interest, such as hospitalisation, requirement of supplemental oxygen or mortality, is not known.*

The Taskforce recognises that subcutaneous casirivimab plus imdevimab may be administered to household contacts who were PCR-negative at the time of testing, but become PCR-positive by the time of receiving casirivimab plus imdevimab. Although the Taskforce does not currently recommend casirivimab plus imdevimab for PCR-positive individuals with asymptomatic or mildly symptomatic COVID-19, this treatment is unlikely to result in harm.

This trial was conducted in a population exposed to a mixture of SARS-CoV-2 variants, but before the emergence and dominance of the Delta variant. The effectiveness of casirivimab plus imdevimab in populations exposed to the Delta variant of SARS-CoV-2 has not been established.

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

Evidence To Decision

Benefits and harms — Substantial net benefits of the recommended alternative

In close household contacts of individuals with confirmed COVID-19, casirivimab plus imdevimab probably decreases the incidence of symptomatic and confirmed COVID-19 infection (symptomatic plus asymptomatic) and probably results in fewer adverse events. It is unclear if casirivimab plus imdevimab makes a difference to all-cause mortality due to few events.

Older people living with frailty or cognitive impairment
People aged over 65 years were included in the trials but no details were reported for frailty or cognitive impairment.

People requiring palliative care

There is uncertainty regarding benefits and harms for people requiring palliative care as no details were reported in the trials for this population. In particular, the benefits for symptom management are uncertain.

Pregnant or breastfeeding women
There is uncertainty around the benefits and harms of casirivimab plus imdevimab for pregnant or breastfeeding women with COVID-19 as no details were reported in the trials for these populations.

Children or adolescents
Children aged 12 years and over were eligible for inclusion in the study on casirivimab plus imdevimab, but results were not presented separately for this subgroup and it is unclear how many children were included. As a result, there remains uncertainty around the benefits and harms of casirivimab plus imdevimab for children and adolescents at risk of COVID-19 infection.

Certainty of the Evidence — Moderate

Certainty of the evidence is moderate for symptomatic COVID-19 infection, confirmed COVID-19 infection and adverse events (due to serious imprecision based on reliance on a single study), and low for all-cause mortality and serious adverse events (due to very serious imprecision based on reliance on a single study, few events and wide confidence intervals).

Referenzen
1. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention.
2. Imprecision: very serious. due to few events, Only data from one study.
3. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention.
4. Imprecision: serious. Only data from one study.
5. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention.
6. Imprecision: serious. Only data from one study.
7. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention.
8. Imprecision: serious. Only data from one study.
9. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention.
10. Imprecision: very serious. Only data from one study, due to few events.
11. Systematic review [547] with included studies: O'Brien 2021. Baseline/comparator: Control arm of reference used for intervention

7.3. Hydroxychloroquine for post-exposure prophylaxis

Not recommended

For people exposed to individuals with SARS-CoV-2 infection, do not use hydroxychloroquine for post-exposure prophylaxis outside of randomised trials with appropriate ethical approval.

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 hydroxychloroquine for post-exposure prophylaxis in these populations unless they are eligible to be enrolled in trials.

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

Evidence To Decision

Benefits and harms — Important harms

General adult population
In addition to uncertainty around the benefits for people exposed to individuals with COVID-19, there are well-known harms, with potentially severe adverse events. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include prolonged QT interval and lowered convulsive threshold. Long-term harms include retinopathy and chronic cardiac myopathy, among several others.

There are several known and potential interactions with other drugs. Although overdose of hydroxychloroquine may have potentially fatal complications, this is unlikely when taken at prophylactic doses.

Children and adolescents
Paediatricians have considerable experience with hydroxychloroquine in children and adolescents for other indications.

Pregnant and breastfeeding women
Hydroxychloroquine is used in pregnant and breastfeeding women for the treatment of malaria and autoimmune diseases. Studies of hydroxychloroquine for these indications have shown a favourable safety profile, though further research is needed.

People requiring palliative care and older people living with frailty or cognitive impairment
There may be additional concerns regarding harms in these populations.

Certainty of the Evidence — Very low

General adult population
Certainty of the evidence for the primary outcome of laboratory-confirmed diagnosis is moderate. Certainty is high for adverse events and low for all other outcomes, due either to serious risk of bias and serious imprecision (symptoms compatible with COVID-19, confirmed or probable infection and discontinuation due to adverse events) or very serious imprecision (all-cause mortality and serious adverse events).

Children and adolescents, pregnant and breastfeeding women, people requiring palliative care and older people living with frailty or cognitive impairment
Certainty of the evidence was downgraded further for all outcomes due to indirectness, as it is unclear whether these special populations were included in the trials.

Referenzen
1. Systematic review [359] with included studies: Mitja 2020, Boulware 2020. Baseline/comparator: Control arm of reference used for intervention.
2. Imprecision: serious. Wide confidence intervals.
3. Systematic review [359] with included studies: Mitja 2020, Boulware 2020. Baseline/comparator: Control arm of reference used for intervention.
4. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Imprecision: serious. Wide confidence intervals.

5. Systematic review [359] with included studies: Boulware 2020. Baseline/comparator: Control arm of reference used for intervention.
6. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Imprecision: serious. Wide confidence intervals.
7. Systematic review [359] with included studies: Boulware 2020, Mitja 2020. Baseline/comparator: Control arm of reference used for intervention.
8. Imprecision: very serious. Only 13 events.
9. Systematic review [359] with included studies: Mitja 2020. Baseline/comparator: Control arm of reference used for intervention.
10. Imprecision: very serious. Only 31 events.
11. Systematic review [359] with included studies: Mitja 2020, Boulware 2020. Baseline/comparator: Control arm of reference used for intervention.
12. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias.
13. Systematic review [359] with included studies: Boulware 2020, Mitja 2020. Baseline/comparator: Control arm of reference used for intervention.
14. Risk of Bias: serious. Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of participants and personnel, resulting in potential for performance bias, Inadequate/lack of blinding of outcome assessors, resulting in potential for detection bias. Imprecision: very serious. Only 33 events.

World Health Organization (WHO), 2021 [3].

WHO Living guideline: Drugs to prevent COVID-19; WHO-2019-nCoV-prophylaxes-2021.1

Zielsetzung/Fragestellung

What is the role of drugs for preventing COVID-19?

Methodik

<u>Grundlage der Leitlinie</u>

- 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.

<u>Recherche/Suchzeitraum:</u>

- living systematic review, letzte Aktualisierung: 02. März 2021

<u>LoE/GoR</u>

- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

<u>Sonstige methodische Hinweise</u>

- This is a living guideline, so the recommendation included here will be updated, and new recommendations will be added on other prophylactic interventions for COVID-19.

Recommendation

7. Recommendations for prophylaxis

7.1 Hydroxychloroquine

Recommendation against — New

We recommend against administering hydroxychloroquine prophylaxis to individuals who do not have COVID-19 (strong recommendation, high certainty evidence).

Remark: This recommendation applies to individuals with any baseline risk of developing COVID-19 and any hydroxychloroquine dosing regimen.

Evidence to decision

Benefits and harms — Substantial net benefits of the recommended alternative

Used prophylactically, hydroxychloroquine has a small or no effect on death and hospital admission (high certainty), and probably has a small or no effect on laboratory-confirmed COVID-19 (moderate certainty). It probably increases the risk of adverse effects leading to discontinuation of the drug (moderate certainty).

There was no subgroup effect according to known exposure to a person with SARS-CoV-2 infection or hydroxychrloroquine dose regimen (extremely low event rates precluded investigation of subgroup effects for mortality). The panel therefore assumed similar relative effects across subgroups.

Certainty of the Evidence — High

For key outcomes of mortality and hospital admission, the panel had high certainty that hydroxychloroquine had no or a small effect. The certainty was moderate for the outcome of laboratory-confirmed COVID-19 due to serious risk of bias (lack of blinding in one trial), and also for adverse effects due to serious imprecision (in this case the panel assessed the certainty that the null effect could be excluded).

Hintergrundinformationen:

The latest evidence: The recommendation on hydroxychloroquine was informed by results from a systematic review and NMA that pooled data from six trials with 6059 participants who did not have COVID-19 and received hydroxychloroquine (3). Three trials enrolled participants who had a known exposure to infection.

The resulting GRADE evidence summary suggested that hydroxychloroquine has a small or no effect on mortality (odds ratio 0.70; 95 % CI 0.24–1.99; absolute effect estimate 1 fewer death per 1000, 95 % CI from 2 fewer – 3 more deaths per 1000 individuals; high certainty evidence) and on admission to hospital (odds ratio 0.87; 95 % CI 0.42–1.77; absolute effect estimate 1 fewer per 1000, 95 % CI 3 fewer – 4 more admissions to hospital per 1000 individuals; high certainty evidence). Hydroxychloroquine probably has a small or no effect on laboratory-confirmed SARS-CoV-2 infection (odds ratio 1.03; 95% CI 0.71–1.47; absolute effect estimate 2 more per 1000; 95 % CI 18 fewer – 28 more infections per 1000 individuals; moderate certainty evidence). In contrast, hydroxychloroquine probably increases adverse events leading to discontinuation (odds ratio 2.34; 95 % CI 0.93–6.08; absolute effect estimate 19 more per 1000, 95 % CI 1 fewer – 70 more adverse events per 1000 individuals; moderate certainty evidence).

There was no indication of a credible subgroup effect based on known exposure to a person with SARS-CoV-2 infection or hydroxychloroquine dosing regimen (extremely low event rates precluded investigation of subgroup effects for mortality).

Referenz:

3. Bartoszko JJ, Siemieniuk R, Kum E, et al. Prophylaxis against covid-19: living systematic review and network meta-analysis. medRxiv 2021.02.24.21250469 2021;Journal

IDSA, 2022 [1].

Infectious Diseases Society of America (IDSA)

Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 6.0.2

Zielsetzung/Fragestellung

Our objective was to develop evidence-based rapid guidelines intended to support healthcare personnel (HCP) in their decisions about infection prevention when caring for patients with suspected or known coronavirus disease 2019 (COVID-19).

Methodik

Grundlage der Leitlinie

Anlage I Repräsentatives Gremium: kein Patientenvertreter;

Anlage II Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;

Anlage III Systematische Suche, Auswahl und Bewertung der Evidenz;

Anlage IV Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: trifft zu;

Anlage V Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;

Anlage VI Regelmäßige Überprüfung der Aktualität gesichert: trifft zu.

Recherche/Suchzeitraum:

Anlage VII 1974 to 2021 March 31.

LoE/GoR

Anlage VIII Risk of bias was assessed using the Cochrane Risk of Bias Tool for RCTs

Anlage IX Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Anlage X As per GRADE methodology, recommendations are labeled as "strong" or "weak/conditional". The words "we recommend" indicate strong recommendations and "we suggest" indicate conditional recommendations. Abbildung 1 provides the suggested interpretation of strong and weak/conditional recommendations for patients, clinicians, and healthcare policymakers. In some situations where the evidence was judged insufficient to provide a clear direction "for" or "against" a particular management strategy, the panel decided to make a "no recommendation."

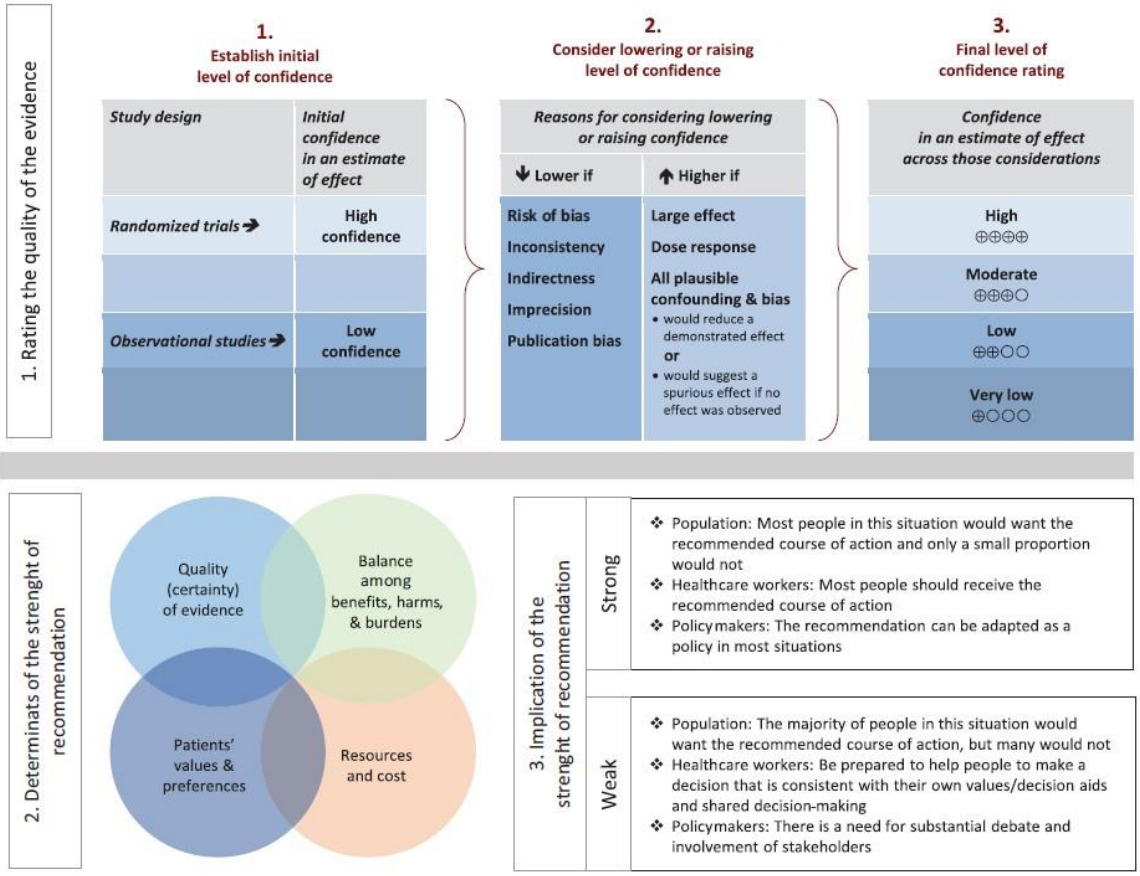

Figure 2. Approach and implications to rating the quality of evidence and strength of recommendations using the Grading of Recommendations Assessment, Development and Evaluation methodology. Unrestricted use of the figure granted by the US GRADE Network.

Sonstige methodische Hinweise

Anlage XI 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

Anlage XII Using a combination of direct and indirect evidence, the panel was able to provide recommendations for 8 specific questions on the use of personal protective equipment (PPE) for HCP who provide care for patients with suspected or known COVID-19. Where evidence was lacking, attempts were made to provide potential avenues for investigation. Significant gaps in the understanding of the transmission dynamics of Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) remain, and PPE recommendations may need to be modified in response to new evidence.

Respirator: Devices used to protect HCP from airborne particles that can lead to infection. This includes N95 filtering facepiece respirators and higher-level "mask-like" respirators (eg, N99, N100) and powered air-purifying respirators (PAPRs) and controlled air-purifying respirators.

Donning and Doffing Procedures: Donning refers to the practice of putting on PPE. Doffing refers to the practice of taking off PPE.

Crisis Standards of Care

Conventional capacity: Usual supplies available and used (1).

Contingency capacity: Conservation, adaptation, and substitution of supplies with occasional reuse of select supplies.

Crisis capacity: Critical supplies lacking. PPE extended use: The use of PPE for greater than a single patient encounter and without removing the PPE, with or without the use of additional devices (eg, a face shield over a surgical mask). Recommended for use only in contingency or crisis capacity settings (3).

PPE reuse: The use of PPE that is doffed after each patient encounter and redonned after a period of time and/or a processing step. Recommended for use only in contingency or crisis capacity settings (3).

Recommendations

Hydroxychloroquine as Post-Exposure Prophylaxis

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)

Neutralizing Antibodies for Pre-Exposure and Post-Exposure Prophylaxis

Section last reviewed and updated 12/23/2021 Last literature search conducted 11/30/2021

- Recommendation 18: In persons exposed to COVID-19 who are at high risk of progression to severe COVID-19, the IDSA guideline panel suggests post-exposure casirivimab/imdevimab rather than no casirivimab/imdevimab. (Conditional recommendation, Low certainty of evidence)

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

Figure 4. FDA EUA criteria for the use of casirivimab/imdevimab for post-exposure prophylaxis of COVID-19 [1]

This EUA is for the use of the unapproved products casirivimab and imdevimab for post-exposure prophylaxis of COVID-19 in adult and pediatric individuals (12 years of age and older weighing at least 40 kg) who are at high risk for progression to severe COVID-19, including hospitalization or death, and are:

- Not fully vaccinated **OR** who are not expected to mount an adequate immune response to complete SARS-CoV-2 vaccination (e.g., individuals with immunocompromising conditions including those taking immunosuppressive medications) **AND**
  - Have been exposed to an individual infected with SARS-CoV-2 consistent with close contact criteria per CDC criteria **OR**
  - Who are at high risk of exposure to an individual infected with SARS-CoV-2 because of occurrence of SARS-CoV-2 infection in other individuals in the same institutional setting (e.g., nursing homes, prisons).

Reference

1. U.S. Food and Drug Administration. Fact Sheet for Health Care Providers: Emergency Use Authorization (EUA) of Regen-CoV™ (casirivimab with imdevimab). Available at: https://www.fda.gov/media/145611/download. Accessed 9 April 2021.

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 1 of 12, January 2022) am 27.01.2022

#	Suchfrage
1	MeSH descriptor: [COVID-19] explode all trees
2	MeSH descriptor: [SARS-CoV-2] explode all trees
3	(Covid* OR 2019ncov OR cov2 OR ncov19 OR sarscov* OR (ncov NEAR/3 2019) OR (ncov NEAR/3 19)):ti,ab,kw
4	(coronavir* OR (corona NEXT vir*) OR betacoronavir* OR (beta NEXT coronavir*) OR SARS*):ti,ab,kw
5	((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis)):ti,ab,kw
6	(wuhan AND (virus* OR viral OR viridae OR pneumonia* OR pneumonitis)):ti,ab,kw
7	("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
8	{OR #1-#7}
9	#8 with Cochrane Library publication date Between Jan 2017 and Jan 2022

Systematic Reviews in Medline (PubMed) am 26.01.2022

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/prevention and control"[MeSH Major Topic]
2	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
3	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])
4	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
5	(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])
6	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(("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]
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR

#	Suchfrage
	postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh])
10	((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR immunization*[ti] OR passive immunization[majr]
11	#9 OR #10
12	#8 AND #11
13	#1 OR #12
14	(#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 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]))

#	Suchfrage
	OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
15	(#14) AND ("2017/01/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT "The Cochrane database of systematic reviews"[Journal]
17	(#16) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 26.01.2022

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/prevention and control"[MeSH Major Topic]
2	COVID-19[MeSH Terms] OR SARS-CoV-2[MeSH Terms]
3	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])
4	Coronavir*[ti] OR corona vir*[ti] OR betacoronavir*[ti] OR beta coronavir*[ti] OR SARS*[ti]
5	(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])
6	(wuhan[tiab]) AND (virus*[ti] OR viral[ti] OR viridae[ti] OR pneumonia*[ti] OR pneumonitis[ti])
7	(("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]
8	#2 OR #3 OR #4 OR #5 OR #6 OR #7
9	(prevent*[ti] OR control*[ti] OR precaution*[ti] OR prophylax*[tiab] OR prophylactic[tiab] OR Pre-Exposure[tiab] OR Preexposure[tiab] OR postexposure[tiab] OR post-exposure[tiab] OR exposed[ti] OR Chemoprevent*[tiab] OR Chemoprophylax*[tiab] OR Chemo-prevent*[tiab] OR Chemo-prophylax*[tiab] OR asymptomatic infection*[tiab] OR Inapparent Infection*[tiab] OR subclinical Infection*[tiab] OR presymptomatic infection*[tiab] OR pre-symptomatic infection*[tiab] OR asymptomatic[ti] OR presymptomatic[ti] OR pre-symptomatic[ti] OR Post-Exposure Prophylaxis[mh] OR Pre-Exposure Prophylaxis[mh] OR Chemoprevention[mh] OR infection control[majr] OR Universal Precautions[majr] OR Asymptomatic Infections[mh])
10	((therap*[ti]) AND (globulin*[ti] OR serum*[ti] OR sero*[ti] OR immunoglobulin*[ti])) OR (Antibod*[tiab] AND transfer*[tiab]) OR serotherap*[ti] OR immunotherap*[ti] OR immunization*[ti] OR passive immunization[majr]
11	#9 OR #10

#	Suchfrage
12	#8 AND #11
13	#1 OR #12
14	(#13) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp]*)*
15	(#14) AND ("2017/01/01"[PDAT] : "3000"[PDAT])
16	(#15) NOT (retracted publication [pt] OR retraction of publication [pt])

Iterative Handsuche nach grauer Literatur, abgeschlossen am 27.01.2022

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

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

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

Referenzen

1. **Infectious Diseases Society of America (IDSA).** Infectious Diseases Society of America guidelines on the treatment and management of patients with COVID-19: version 6.0.2 [online]. 03.02.2022. Arlington (USA): IDSA; 2022. [Zugriff: 18.02.2022]. URL: https://www.idsociety.org/globalassets/idsa/practice-guidelines/covid-19/treatment/idsa-covid-19-gl-tx-and-mgmt-v6.0.2.pdf.
2. **National COVID-19 Clinical Evidence Taskforce.** Australian guidelines for the clinical care of people with COVID-19: version 51.0 [online]. 18.02.2022. Melbourne (AUS): National COVID-19 Clinical Evidence Taskforce; 2022. [Zugriff: 18.02.2022]. URL: https://files.magicapp.org/guideline/21052a5c-3014-48ae-8585-edad2ee2e716/published_guideline_6050-51_0.pdf.
3. **World Health Organization (WHO).** WHO living guideline: drugs to prevent Covid-19; WHO-2019-nCoV-prophylaxes-2021.1 [online]. 02.03.2021. Genf (SUI): WHO; 2021. [Zugriff: 18.02.2022]. URL: https://apps.who.int/iris/rest/bitstreams/1334211/retrieve.

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

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

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

Kontaktdaten

Namen aller beteiligten Fachgesellschaften:

Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)

Deutsche Gesellschaft für Infektiologie (DGI)

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)

Indikation gemäß Beratungsantrag

Post-Expositions-Prophylaxe zur Reduktion des Risikos einer COVID-19 Infektion (laborbestätigte SARS-CoV-2-Infektion mit Symptomen) bei Erwachsenen

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

Die Post-Expositions-Prophylaxe gehört unter den Bedingungen der Omikron-Welle nicht zur regelhaften Versorgungspraxis in Deutschland. Sie wird weder in der 22. Version der S2e-Leitlinie der DEGAM, deren Empfehlungen im Konsens mit 8 anderen Fachgesellschaften* erstellt wurden [1], noch in der in Überarbeitung befindlichen S3-Leitlinie empfohlen [2].

Die Gründe lassen sich wie folgt zusammenfassen:

- Von den in Deutschland zur Verfügung stehenden monoklonalen Antikörpern ist nur Sotrovimab gegen die Omikronvariante des SARS-CoV-2-Virus wirksam [3, 4]. Zur Wirksamkeit einer Post-Expositionsprophylaxe mit Sotrovimab liegen keine publizierten RCT vor.
- Ebenso liegen keine Studien zur Wirksamkeit anderer medikamentöser Therapieoptionen gegen COVID-19 als Post-Expositionsprophylaxe vor.
- Die vorliegenden Studien zur Post-Expositionsprophylaxe zeigen eine signifikante Reduktion von COVID-19 Erkrankungen und SARS-CoV2-Infektionen bei PCR-negativen und seronegativen Patientinnen und Patienten bei Verwendung von Casirivimab und Imdevimab (s.c.) [5] bzw. Bamlanivimab [6]. Da weder Casirivimab und Imdevimab, noch Bamlanivimab in vitro eine ausreichende Wirksamkeit gegen Omikron zeigen, haben diese Studien derzeit keine Relevanz.

* DGIIN, DGI, DGP, DGIM, DGPI, DGRh, DGKJ, DAIG

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Post-Expositions-Prophylaxe zur Reduktion des Risikos einer COVID-19 bei Erwachsenen, die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Wie oben geschildert, wird die Post-Expositions-Prophylaxe nicht regelhaft angewandt. Sie ist denkbar (als Off-Label-Use) im Rahmen von Einzelfallentscheidungen, z.B. bei Exposition stark immunsupprimierter Patientinnen und Patienten, bei denen eine relevante Beeinträchtigung der Impfantwort zu erwarten ist.

Kontaktdaten

Namen aller beteiligten Fachgesellschaften:

Deutsche Gesellschaft für Allgemeinmedizin und Familienmedizin (DEGAM)

Deutsche Gesellschaft für Infektiologie (DGI)

Deutsche Gesellschaft für Internistische Intensivmedizin und Notfallmedizin (DGIIN)

Indikation gemäß Beratungsantrag

Post-Expositions-Prophylaxe zur Reduktion des Risikos einer COVID-19 Infektion (laborbestätigte SARS-CoV-2-Infektion mit Symptomen) bei Erwachsenen

Ein Hinweis für den zukünftigen Einsatz von Medikamenten als Post-Expositionsprophylaxe

Bei Entwicklung und Verbreitung neuer SARS-CoV-2-Varianten müssten die monoklonalen Antikörper, als auch andere potenzielle Therapeutika auf ihre Wirksamkeit im Rahmen einer Post-Expositionsprophylaxe geprüft werden. Dabei wird zu erwägen sein, bei welcher Patientengruppe die Wirksamkeit zu untersuchen ist, denn seronegative Patientinnen und Patienten wird es kaum (noch) geben. Auch kann bei Wirksamkeit nur gegen bestimmte Virusvarianten und ein paralleles Vorkommen mehrerer Varianten in der Bevölkerung die Praktikabilität des Einsatzes der Medikamente als Post-Expositionsprophylaxe durch die Notwendigkeit beeinträchtigt sein, die Virusvariante vorab bestimmen zu müssen.

[1] Informationen & Praxishilfen für niedergelassene Hausärztinnen und Hausärzte, S2e-Leitlinie, Living Guideline (https://www.awmf.org/leitlinien/detail/ll/053-054.html)

[2] Empfehlungen zur stationären Therapie von Patienten mit COVID-19 - Living Guideline (https://www.awmf.org/leitlinien/detail/ll/113-001LG.html)

[3] Cameroni E, Bowen JE, Rosen LE et al. Broadly neutralizing antibodies overcome SARS-CoV-2 Omicron antigenic shift. Nature 2022; 602: 664-670. doi: 10.1038/s41586-021-04386-2. Epub 2021 Dec 23.

[4] Hoffmann M, Krüger N, Schulz S et al. The Omicron variant is highly resistant against antibody-mediated neutralization: Implications for control of the COVID-19 pandemic. Cell 2022; https://doi.org/10.1016/j.cell.2021.12.032

[5] O'Brien MP, Forleo-Neto E, Musser BJ, et al.: Subcutaneous REGEN-COV Antibody Combination to Prevent Covid-19. N Engl J Med 2021 ; 385:1184-1195. DOI: 10.1056/NEJMoa2109682

[6] Cohen MS et al. Effect of Bamlanivimab vs Placebo on Incidence of COVID-19 Among Residents and Staff of Skilled Nursing and Assisted Living Facilities: A Randomized Clinical Trial. JAMA. 2021;326(1):46–55. doi:10.1001/jama.2021.8828