Gemeinsamer Bundesausschuss

Kriterien zur Bestimmung der zweckmäßigen Vergleichstherapie

und

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

Vorgang: 2020-B-180 Remdesivir

Stand: Juli 2020

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

Remdesivir
Behandlung der Coronavirus-Erkrankung 2019 (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	Es liegen keine Beschlüsse vor.
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 N.N. Veklury	Behandlung der Coronavirus-Erkrankung 2019 (COVID 19) bei Erwachsenen und Jugendlichen (ab einem Alter von 12 Jahren und einem Körpergewicht von mindestens 40 kg) mit einer Pneumonie mit Bedarf an zusätzlicher Sauerstoffversorgung.
	Es ist kein Arzneimittel im vorliegenden Anwendungsgebiet zugelassen.

Quellen: AMIS-Datenbank, Fachinformationen

Gemeinsamer Bundesausschuss

Abteilung Fachberatung Medizin

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

Vorgang: 2020-B-180 (Remdesivir)

Auftrag von:	Abt. AM
Bearbeitet von:	Abt. FB Med
Datum:	10. Juli 2020

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Abkürzungsverzeichnis

ARDS	Acute Respiratory Distress Syndrome
AWMF	Arbeitsgemeinschaft der wissenschaftlichen medizinischen Fachgesellschaften
CoV	Coronavirus
COVID-19	Coronavirus Disease 2019
ECMO	Extracorporeal Mechanical Oxygenation
ECRI	ECRI Guidelines Trust
G-BA	Gemeinsamer Bundesausschuss
GIN	Guidelines International Network
GoR	Grade of Recommendations
GRADE	Grading of Recommendations, Assessment, Development, and Evaluation
HFNC	High-Flow Nasal Cannula
HR	Hazard Ratio
ICU	Intensive Care Unit
IDSA	Infectious Diseases Society of America
IQWiG	Institut für Qualität und Wirtschaftlichkeit im Gesundheitswesen
KI	Konfidenzintervall
LoE	Level of Evidence
MAGICapp	Making GRADE the Irresistible Choice
MD	Mean Difference
MERS	Middle East Rrespiratory Syndrome
NICE	National Institute for Health and Care Excellence
NIPPV	Non-Invasive Positive Pressure Ventilation
NMBA	Neuromuscular blocking agents
OR	Odds Ratio
PEEP	Positive Endexpiratory Pressure
Pplat	Plateau pressures
RCT	Randomized Controlled Trial
ROBINS-I	Risk of Bias Instrument for Non-randomized Studies – of Interventions
RR	Relatives Risiko
SARS-CoV-2	Severe Acute Respiratory Syndrome Coronavirus 2
SIGN	Scottish Intercollegiate Guidelines Network
SpO_2	percentage of oxyhemoglobin saturation
SSC	Surviving Sepsis Campaign
TRIP	Turn Research into Practice Database
WHO	World Health Organization

1 Indikation

Patienten mit SARS – CoV 2 Infektion symptomatisch mit Pneumonie, + /- Beatmung sowie +/ - Sauerstoffgabe.

2 Systematische Recherche

Es wurde eine systematische Literaturrecherche nach systematischen Reviews, Meta-Analysen und evidenzbasierten systematischen Leitlinien zur Indikation SARS-CoV-2-Infektion/COVID-19 durchgeführt. Der Suchzeitraum wurde auf die letzten 5 Jahre eingeschränkt und die Recherche am 29.06.2020 abgeschlossen. Die Suche erfolgte in den aufgeführten Datenbanken bzw. Internetseiten folgender Organisationen: The Cochrane Library (Cochrane Database of Systematic Reviews), MEDLINE (PubMed), AWMF, ECRI, G-BA, GIN, NICE, TRIP, SIGN, WHO. Ergänzend erfolgte eine freie Internetsuche nach aktuellen deutschen und europäischen Leitlinien. Die detaillierte Darstellung der Suchstrategie ist am Ende der Synopse aufgeführt.

In einem zweistufigen Screening wurden die Ergebnisse der Literaturrecherche bewertet. Die Recherche ergab 1425 Quellen. Im ersten Screening wurden auf Basis von Titel und Abstract nach Population, Intervention, Komparator und Publikationstyp nicht relevante Publikationen ausgeschlossen. Zudem wurde eine Sprachrestriktion auf deutsche und englische Quellen vorgenommen. Im zweiten Screening wurden die im ersten Screening eingeschlossenen Publikationen als Volltexte gesichtet und auf ihre Relevanz und methodische Qualität geprüft. Dafür wurden dieselben Kriterien wie im ersten Screening sowie Kriterien zur methodischen Qualität der Evidenzquellen verwendet. Basierend darauf, wurden insgesamt 13 Quellen eingeschlossen. Es erfolgte eine synoptische Darstellung wesentlicher Inhalte der identifizierten Referenzen.

3 Ergebnisse

3.1 G-BA Beschlüsse/IQWiG Berichte

Es konnten keine relevanten G-BA Beschlüsse identifiziert werden.

3.2 Cochrane Reviews

Es konnten keine relevanten Cochrane Reviews identifiziert werden.

3.3 Systematische Reviews

Es sind bislang keine medikamentösen Therapien in dieser Indikation zugelassen. Dargestellt wird der Systematische Review von Liu et al., 2020, der die Evidenz aus den zitierten RCTs der Leitlinien darstellt.

Liu W et al., 2020 [7].

Siehe auch: Chodhury MS et al., 2020 [2]; Das S et al., 2020 [3]; Ford N et al., 2020 [4]; Hernandes AV et al., 2020 [5]; Rodrigo C et al, 2020 [9]; Sarma P et al., 2020 [10]; Singh AK et al., 2020 [11]; Zhong H et al, 2020 [13];

Efficacy and safety of antiviral treatment for coronavirus disease 2019 (COVID-19) from evidence in studies of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and other acute viral infections: a systematic review and meta-analysis

Fragestellung

We provide a systematic review conducted to support a clinical practice guideline that offers recommendations to address currently used antiviral treatments for COVID-19**.**

Methodik

Population:

- Patients enrolled in the trial had a diagnosis of COVID-19, SARS, Middle East respiratory syndrome (MERS) or other acute respiratory infectious diseases

Intervention/Komparator:

- Favipiravir vs. umifenovir
- Hydroxychloroquine vs. no hydroxychloroquine
- Hydroxychloroquine + interferon vs. interferon
- Lopinavir/ritonavir vs. no lopinavir/ritonavir
- Umifenovir versus no umifenovir

Endpunkte:

- Mortality, mechanical ventilation and length of stay in the intensive care unit (ICU) were assessed only for the population of patients with severe illness, whereas we assessed rate of disease progression and symptom-based outcomes for only the nonsevere population.

Recherche/Suchzeitraum:

- We searched MEDLINE, Embase, the Cochrane Central Register of Controlled Trials (CENTRAL), PubMed and 3 Chinese databases (China National Knowledge Infrastructure [CNKI], Wanfang and SinoMed) through Apr. 19, 2020, and medRxiv and Chinaxiv preprints through Apr. 27, 2020. We also searched another Chinese database (Chongqing VIP Information) through Apr. 30, 2020.

Qualitätsbewertung der Studien:

- Risk of bias for each study were assessed using a modification of the Cochrane criteria for RCTs
- Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) approach informed the assessment of quality of evidence for each of our outcomes

Table 1: Definitions of quality of evidence[13]

Quality	Definition
High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	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	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.

Ergebnisse

Es werden nur die Ergebnisse der eingeschlossenen RCTs mit Covid 19-Patienten (n=6) dargestellt!

Anzahl eingeschlossener Studien:

- 19 Studies (7 RCTs: 6 RCTs for Covid-19, 1 RCT for Influenza with unspecified severity)

Charakteristika der Population:

Abbildung 1: Characteristics of the 6 RCTs for COVID-19

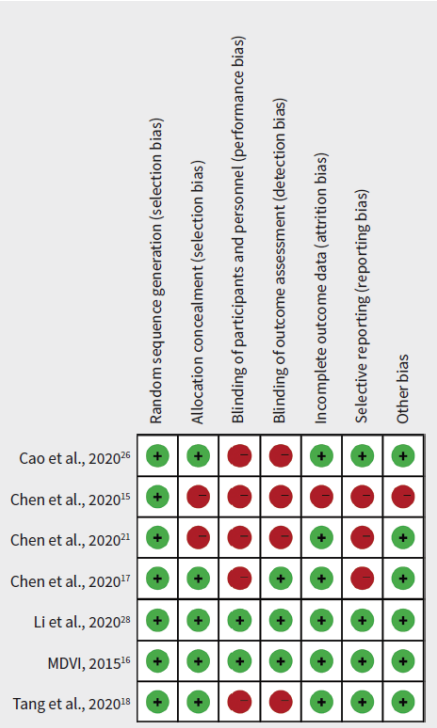
Reference	Dosage and administration: Study intervention	Dosage and administration: Antiviral agent comparison	Study design	Country	Participant population	No. of participants	Age, mean ± SD*	Percentage of population who were male	Percentage of population with severe disease
Favipiravir versus umifenovir									
Chen et al., 2020[15]‡	Favipiravir 1600 mg po b.i.d. on day 1 and 600 mg po b.i.d. for 7–10 d§	Umifenovir (200 mg) po t.i.d. for 7–10 d	RCT	China	COVID-19 with mixed severity	236	NR	46.6	11.4
Hydroxychloroquine versus no hydroxychloroquine									
Chen et al., 2020[17]‡	Hydroxychloroquine (200 mg) po b.i.d. for 5 d	No hydroxychloroquine	RCT	China	Nonsevere COVID-19	62	44.7 ± 15.3	46.8	0
Tang et al., 2020[18]‡	Hydroxychloroquine: loading dose of 1200 mg daily for 3 d followed by a maintainence dose of 800 mg daily for remaining treatment days (total treatment duration: 2 wk for patients with mild/ moderate disease or 3 wk for patients with severe disease)	No hydroxychloroquine	RCT	China	COVID-19 with mixed severity	150	46.1 ± 14.7	54.7	1.3
Hydroxychloroquine plus interferon versus interferon alone									
Chen et al., 2020[21]	Hydroxychloroquine (400 mg) po daily for 5 d plus interferon-α by aerosol inhalation (80.0% of patients used umifenovir)	Interferon-α by aerosol inhalation (66.7% of patients used umifenovir and 13.3% used lopinavir/ ritonavir)	RCT	China	Nonsevere COVID-19	30	48.6 ± 4.1	70.0	0
Lopinavir/ritonavir versus no lopinavir/ritonavir									
Cao et al., 2020[26]	Lopinavir/ritonavir (400/100 mg) po b.i.d. for 14 d	No lopinavir/ritonavir	RCT	China	Severe COVID-19	199	58.0 (49.0–68.0)†	60.3	100.0
Lopinavir/ritonavir versus no lopinavir/ritonavir, umifenovir versus no umifenovir									
Li et al., 2020[28]‡	A: lopinavir/ritonavir (200 mg/50 mg) 500 mg po q.12h for 7–14 d B: umifenovir (200 mg) po t.i.d. for 7–14 d	No lopinavir/ritonavir or umifenovir	RCT	China	Nonsevere COVID-19	44	49.4 ± 14.9	47.7	0

Note: b.i.d. = twice a day, COVID-19 = coronavirus disease 2019, im = intramuscular, IQR = interquartile range, MERS = Middle East respiratory syndrome, NR = not reported, po = by mouth, q.6h = every 6 hours, q.8h = every 8 hours, q.12h = every 12 hours, RCT = randomized controlled trial, SARS = severe acute respiratory syndrome, sc = subcutaneous, SD = standard deviation, t.i.d. = 3 times per day.
*Unless stated otherwise.
†Median (IQR).
‡ Preprint.
§The course of treatment in both groups was 7–10 days. If necessary, the treatment time could have been extended to 10 days according to the judgment of researchers.
¶Mean (range).
**Only 155 of 183 participants received this treatment regimen; the other 28 patients received several lower-dose treatment regimens.
††Calculated from the baseline characteristic, admission oxygen saturation < 95%.

Qualität der Studien:

Abbildung 2: Risk-of-bias assessment for included randomized controlled trials.

(Note: References 15, 17, 18 and 28 are preprints.)



Studienergebnisse:

Hydroxychloroquine:

- Three RCTs[17,18,21] (2 of these RCTs are preprints17,18) that involved 240 patients with nonsevere and 2 patients with severe COVID-19 illness compared treatment with hydroxychloroquine and treatment without hydroxychloroquine, providing very low-quality evidence of minimal effects on viral clearance at day 14 (RR 0.98, 95% CI 0.89 to 1.07), progression from nonsevere to severe illness (RR 0.96, 95% CI 0.10 to 9.66) or clinical recovery at day 7 (RR 1.10, 95% CI 0.44 to 2.77).[17]
- Hydroxychloroquine might result in a shorter duration of fever (mean difference [MD] 1 d shorter, 95% CI 0.36 to 1.64 d shorter; very low-quality evidence).
- Safety:
  - Two RCTs[18,21] (1 of these studies is a preprint18) that enrolled 178 patients with nonsevere and 2 patients with severe COVID-19 illness reported that no patient had diarrhea in the treatment group without hydroxychloroquine; however, 10.6% (95% CI 4.0% to 17.1%) of patients in the hydroxychloroquine treatment group had diarrhea (low-quality evidence).
  - An RCT that involved 62 patients with nonsevere COVID-19 illness (preprint)[17] reported an incidence of headache or rash in the intervention group of 3.2% (95% CI 0% to 9.4%), with none of these events in the control group.
  - An RCT (preprint)[18] that enrolled 148 patients with nonsevere and 2 with severe COVID-19 reported an incidence of both nausea and blurred vision in 1.4% (95% CI 0% to 4.2%)

of patients and an incidence of vomiting in 2.9% (95% CI 0% to 6.8%); none of these events occurred in the control group. The quality of evidence for headache, rash, nausea, vomiting and blurred vision was very low.

Umifenovir:

- One RCT that enrolled 23 patients with nonsevere COVID-19 illness (preprint)[28] provided limited evidence of uncertain effects of treatment using umifenovir on viral clearance at day 14, cough alleviation at day 7, fever at day 7 and progression to severe illness. With additional indirectness,this trial reported even lower-quality evidence for delayed viral clearance in patients with severe COVID-19 illness.
- Safety: no patients in either the treatment or control groups had diarrhea or decreased appetite (very low quality evidence).

Favipiravir:

- One RCT that enrolled 236 patients (preprint)[15] with mixed-severity COVID-19 illness (88.6% were nonsevere) compared favipiravir with umifenovir and reported a possible increase in clinical recovery at day 7 with favipiravir (RR 1.18, 95% CI 0.95 to 1.48, very low-quality evidence).

Lopinavir/ritonavir:

- One RCT that enrolled 199 patients with severe COVID-19 (preprint)[26] compared treatment with lopinavir/ritonavir with no lopinavir/ritonavir treatment and reported on mortality, viral clearance at day 14, mechanical ventilation and length of stay inICU and hospital. Another RCT compared treatment with lopinavir/ ritonavir with no lopinavir/ritonavir treatment in 28 patients with nonsevere COVID-19 (preprint)[28] and reported on mortality, viral clearance at day 14, cough alleviation at day 7, progression from nonsevere to severe illness and fever at day 7. Because no patients died in the latter RCT, we included only mortality data from the RCT involving patients with severe illness.
- For nonsevere COVID-19 patients, lopinavir/ritonavir may provide little or no reduction in viral clearance at day 14 (RD –0.7%, 95% CI –17.1% to 20.7%, low-quality evidence;[26] [preprint][28]).
- Safety: One RCT that involved 194 patients with severe COVID-19[26] and another RCT that involved 28 patients with nonsevere COVID-19 (preprint)[28] reported no diarrhea in their control groups. The incidence of diarrhea in the intervention group was 6.0% (95% CI 1.7% to 10.4%,[26] (preprint)[28] moderate-quality evidence).
- The RCT with 194 patients[26] reported that lopinavir/ritonavir probably increased nausea (MD 9.5%, 95% CI 3.6% to 15.4%) and vomiting (MD 6.3%, 95% CI 1.4% to 11.2%) (both moderate-quality evidence). This study also reported very low-quality evidence that raised the possibility of an increase in stomach ache.

Anmerkung/Fazit der Autoren

This review provides evidence to support COVID-19 guideline recommendations. To date, persuasive evidence of important benefit does not exist for any antiviral treatment, although important benefit has not been excluded for each agent. Owing to the very low risk of death in patients with nonsevere COVID-19, antiviral treatment will not result in important reductions to mortality in these patients. Confident administration of any antiviral treatment requires the conduct of RCTs showing patient-relevant benefits.

Kommentare zum Review

Because remdesivir was unavailable at the time the panel determined the scope of the guideline, we did not include it in our review; however, results for the first randomized controlled trials (RCTs) of remdesivir are now available.

Referenzen:
15. Chen C, Zhang y, Huang J, et al. Favipiravir versus arbidol for COVID-19: a randomized clinical trial [preprint]. medRxiv 2020 Apr. 15. doi: 10.1101 /2020.03.17.20037432
17. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial [preprint]. medRxiv 2020 Apr. 10. doi: 10.1101/2020.03.22.20040758.
18. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with COVID-19: an open-label, randomized, controlled trial [preprint]. medRxiv 2020 May 7. doi:10.1101/2020.04.10.20060558.
21. Chen J, Liu D, Liu L, et al. A pilot study of hydroxychloroquine in treatment of patients with common coronavirus disease-19 (COVID-19). J Zhejiang Univ 2020;49. doi: 10.3785/j.issn.1008-9292.2020.03.03.
26. Cao B, Wang Y, Wen D, et al. A trial of lopinavir–ritonavir in adults hospitalized with severe COVID-19. N Engl J Med 2020;382:1787-99.
28. Li Y, Xie Z, Lin W, et al. An exploratory randomized, controlled study on the efficacy and safety of lopinavir/ritonavir or arbidol treating adult patients hospitalized with mild/moderate COVID-19 (ELACOI) [preprint]. medRxiv 2020 Apr. 15. doi:10.1101/2020.03.19.20038984.

3.4 Leitlinien

Alhazzani W et al., 2020 [1].

European Society of Intensive Care Medicine and the Society of Critical Care Medicine

Surviving Sepsis Campaign: guidelines on the management of critically ill adults with Coronavirus Disease 2019 (COVID-19)

Zielsetzung/Fragestellung

This guideline provides recommendations to support hospital clinicians managing critically ill adults with COVID-19 in the intensive care unit (ICU).

Methodik

Grundlage der Leitlinie

- Repräsentatives Gremium: The Surviving Sepsis Campaign (SSC) COVID-19 subcommittee
- selected panel members in such a way as to obtain a balance of topic expertise, geographic location and, as far as possible, gender.
- Interessenkonflikte und finanzielle Unabhängigkeit dargelegt: trifft zu;
- Systematische Suche, Auswahl und Bewertung der Evidenz: trifft zu;
- Formale Konsensusprozesse und externes Begutachtungsverfahren dargelegt: The final list of recommendations was developed by panel discussion and consensus; voting on recommendations was not required.;
- Empfehlungen der Leitlinie sind eindeutig und die Verbindung zu der zugrundeliegenden Evidenz ist explizit dargestellt: trifft zu;
- Regelmäßige Überprüfung der Aktualität gesichert: trifft zu: We will have periodic automated electronic searches sent to assigned panel members every week to identify relevant new evidence as it emerges. Accordingly, we will issue further guideline releases in order to update the recommendations, if needed, or formulate new ones.

Recherche/Suchzeitraum:

- we electronically searched major databases, i.e. Cochrane Central and MEDLINE, to identify relevant systematic reviews, randomized controlled trials (RCTs), observational studies, and case series. These electronic searches were performed looking for studies published in English from inception to March 2020.

LoE

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

GoR

- We use the wording "we recommend" for strong recommendations and "we suggest" for suggestions (i.e. weak recommendations). The implications of the recommendation strength are presented in Table 1.

Tabelle 1: Implications of different recommendations to key stakeholders

Recommendation	Meaning	Implications to patients	Implications to clinicians	Implications to policymakers
Strong recommendation or Best practice statement	Must do or Must avoid	Almost all individuals in this situation would want the recommended intervention, and only a small proportion would not want it	Most individuals should receive the recommended course of action	Can be adapted as policy in most situations, including the use as performance indicators
Weak recommendation	Consider doing or Consider avoiding	The majority of individuals in this situation would want the recommended intervention, but many would not	Different choices are likely to be appropriate for different patients, and the recommendation should be tailored to the individual patient's circumstances. Such as patients', family's, or substitute decision maker's values and preferences	Policies will likely be variable

Sonstige methodische Hinweise

- **Using indirect evidence:** Given the recent emergence of COVID-19, we anticipated that there would be a scarcity of direct evidence, and therefore used a predefined algorithm to decide whether indirect evidence could inform a specific question. The SSC COVID-19 panel decided which population to extrapolate evidence from based on the context of the recommendation, and the likelihood of the presence of an effect modifier. Accordingly, we used, as sources of indirect evidence, data on Middle East Respiratory Syndrome Coronavirus (MERS-CoV), Severe Acute Respiratory Syndrome (SARS), and other coronaviruses; in the same way, we considered, as indirect evidence, published data on supportive care in the ICU from studies on influenza and other respiratory viral infections, acute respiratory distress syndrome (ARDS) and sepsis.
- **Conflicts of interest:** Dr. Yaseen Arabi is the principal investigator on a clinical trial for lopinavir/ ritonavir and interferon in Middle East respiratory syndrome (MERS) and he was a nonpaid consultant on antiviral active for MERS-coronavirus (CoV) for Gilead Sciences and SAB Biotherapeutics. He is an investigator on REMAP-CAP trial and is a Board Members of the International Severe Acute Respiratory and Emerging Infection Consortium (ISARIC).

Recommendations

III. Supportive care

Ventilatory support

23. In adults with COVID-19, we **suggest** starting supplemental oxygen if the peripheral oxygen saturation (SpO_2) is < 92% (weak recommendation, low-quality evidence), and recommend starting supplemental oxygen if SpO_2 is < 90%.

Strong recommendation, moderate quality evidence.

24. In adults with COVID-19 and **acute hypoxemic respiratory failure on oxygen**, we recommend that SpO_2 be maintained no higher than 96%.

Strong recommendation, moderate quality evidence.

25. For adults with COVID-19 and **acute hypoxemic respiratory failure** despite conventional oxygen therapy, we **suggest using** high-flow nasal cannula (HFNC) over conventional oxygen therapy.

Weak recommendation, low-quality evidence.

26. In adults with COVID-19 and **acute hypoxemic respiratory failure**, we **suggest** using HFNC over NIPPV.

Weak recommendation, low-quality evidence.

27. In adults with COVID-19 and **acute hypoxemic respiratory failure**, if HFNC is not available and there is no urgent indication for endotracheal intubation, we **suggest** a trial of non-invasive positive pressure ventilation (NIPPV) with close monitoring and short-interval assessment for worsening of respiratory failure.

Weak recommendation, low-quality evidence.

28. **We were not able to make a recommendation** regarding the use of helmet NIPPV compared with mask NIPPV. It is an option, but we are not certain about its safety or efficacy in COVID-19.

29. In adults with COVID-19 receiving NIPPV or HFNC, we **recommend** close monitoring for worsening of respiratory status, and early intubation in a controlled setting if worsening occurs.

Best practice statement.

Invasive Mechanical Ventilation

30. In mechanically ventilated adults with COVID-19 and ARDS, we **recommend** using low tidal volume (Vt) ventilation (Vt 4–8 mL/kg of predicted body weight), over higher tidal volumes (Vt > 8 mL/kg).

Strong recommendation, moderate quality evidence.

31. For mechanically ventilated adults with COVID-19 **and ARDS**, we **recommend** targeting plateau pressures (Pplat) of < 30 cm H_2O

Strong recommendation, moderate quality evidence.

32. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we **suggest** using a higher positive endexpiratory pressure (PEEP) strategy, over a lower PEEP strategy.

Weak recommendation, low-quality evidence.

Remarks: If using a higher PEEP strategy (i.e. PEEP > 10 cm H2O), clinicians should monitor patients for barotrauma

33. For mechanically ventilated adults with COVID-19 and ARDS, we **suggest** using a conservative fluid strategy over a liberal fluid strategy.

Weak recommendation, low-quality evidence.

34. For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we **suggest** prone ventilation for 12–16 h, over no prone ventilation.

Weak recommendation, low-quality evidence.

35. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS:

35.1. Neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation.

Weak recommendation, low-quality evidence.

35.2. In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, we **suggest** using a continuous NMBA infusion for up to 48 h.

Weak recommendation, low-quality evidence.

36. In mechanically ventilated adults with COVID-19 ARDS, we **recommend against** the routine use of inhaled nitric oxide.

Strong recommendation, low-quality evidence.

37. In mechanically ventilated adults with COVID-19, severe ARDS and hypoxemia despite optimizing ventilation and other rescue strategies, we **suggest** a trial of inhaled pulmonary vasodilator as a rescuetherapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off.

Weak recommendation, low-quality evidence.

38. For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, we **suggest** using recruitment maneuvers, over not using recruitment maneuvers.

Weak recommendation, low-quality evidence.

39. If recruitment maneuvers are used, we **recommend against** using staircase (incremental PEEP) recruitment maneuvers.

Strong recommendation, low-quality evidence.

40. In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we **suggest** using venovenous (VV) extracorporeal mechanical oxygenation (ECMO) if available, or referring the patient to an ECMO center.

Weak recommendation, low-quality evidence.

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

IV. COVID-19 therapy

41. In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), **we suggest against** the routine use of systemic corticosteroids.

Weak recommendation, low-quality evidence.

42. In mechanically ventilated adults with COVID-19 **and ARDS**, we **suggest** using systemic corticosteroids, over not using corticosteroids.

Weak recommendation, low-quality evidence.

Remark: The majority of our panel support a weak recommendation (i.e. suggestion) to use steroids in the sickest patients with COVID-19 and ARDS. However, because of the very low-quality evidence, some experts on the panel preferred not to issue a recommendation until higher quality direct evidence is available.

Rationale

There are no controlled clinical trials on the use of corticosteroids in COVID-19 patients or other coronaviruses. A published, but not peer-reviewed, report of 26 patients with severe COVID-19 reports that the use of methylprednisolone at 1–2 mg/kg/day for 5–7 days was associated with shorter duration of supplemental oxygen use (8.2 days vs. 13.5 days; $p < 0.001$) and improved radiographic findings [142]. Although interesting, we judged these preliminary reports to be an insufficient basis for formulating recommendations, due to the risk of confounding. Therefore, we used indirect evidence from community acquired pneumonia, ARDS, and other viral infections to inform our recommendation.

There are several RCTs on the use of systemic corticosteroids in hospitalized patients with community-acquired pneumonia, mostly non-ICU patients, some with sepsis or septic shock. A systematic review and meta-analysis of RCTs showed that using corticosteroids may reduce the need for mechanical ventilation (5 RCTs; 1060 patients; RR 0.45, 95% CI 0.26–0.79), ARDS (4 RCTs; 945 patients; RR 0.24, 95% CI 0.10–0.56) and the duration of hospitalization (6 RCTs; 1499 patients; MD − 1.00 day, 95% CI, − 1.79 to − 0.21), but increase the risk of hyperglycemia requiring treatment [143]. However, these trials included different populations, the effect on mortality outcome was unclear, and they used different drugs and dosing regimens. In addition, there are some concerns about corticosteroid use in viral pneumonias. Therefore, the results may not be generalizable to the COVID-19 population.

There are many published observational studies on the use of steroids in viral pneumonias (i.e. influenza virus, coronaviruses, and others), but they are prone to confounding, as sicker patients usually receive corticosteroids.

We updated a recent Cochrane review on the use of corticosteroids in influenza [144] and searched for studies on other coronaviruses. We included a total of 15 cohort studies on influenza and 10 on coronaviruses. Our meta-analysis of adjusted ORs showed an association between corticosteroid use and increased mortality (OR 2.76, 95% CI 2.06–3.69), but the effect in the patients with other coronaviruses was unclear (OR 0.83, 95% CI 0.32–2.17). Also, these studies are limited by significant heterogeneity. We found significant homogeneity between observational studies on the use of corticosteroids in ARDS caused by coronaviruses and in general viral ARDS (I^2 = 82% and 77% respectively). Furthermore, in both cases, the summary statistic tended toward harm with the use of steroids.

We updated a recent Cochrane review [145] and identified an additional RCT [146] dealing with ARDS. Overall, we included 7 RCTs enrolling 851 patients with ARDS. The use of corticosteroids reduced mortality (RR 0.75, 95% CI 0.59–0.95) and duration of mechanical ventilation (MD − 4.93 days, 95% CI − 7.81 to − 2.06). However, these trials were not focused on viral ARDS, which limits the generalizability of their results to COVID-19 patients. In addition, we reviewed observational studies on corticosteroid use in viral ARDS, and identified 4 cohort studies. Although the point estimate showed increased mortality, the CI included substantial harm and benefit (OR 1.40, 95% CI 0.76–2.57). In a recent RCT (INTEREST trial), the use of recombinant interferon β1b (rIFN β1ba) did not reduce mortality in ARDS patients, but in the subgroup of patients receiving corticosteroids, rIFN β1ba use was associated with increased mortality (OR, 2.53, 95% CI 1.12–5.72) [147]. The only direct evidence comes from a retrospective cohort study of 201 patients with COVID-19 pneumonia. This study showed an association between corticosteroid use and lower mortality in patients with COVID-19 and ARDS (HR 0.38, 95% CI 0.20–0.72). However, the estimate was not adjusted for confounding factors [148].

The effect of corticosteroids in COVID-19 patients with sepsis or septic shock may be different. Recent systematic reviews and meta-analyses of RCTs in sepsis showed small improvements in mortality and faster resolution of shock with corticosteroid use, compared with not using corticosteroids [63, 149, 150] (see the previous section on hemodynamic support).

It is widely recognized that corticosteroids have a range of adverse effects. In viral pneumonia in the ICU, several studies showed increase in viral shedding with corticosteroid use [151–153], potentially indicating viral replication, but the clinical implication of increased viral shedding is uncertain.

Considering the above, the panel issued a suggestion against the routine use of systemic corticosteroids for respiratory failure in COVID-19, and a suggestion to use corticosteroids in the sicker population of COVID-19 with ARDS. If clinicians use corticosteroids in ARDS, they should use lower dosing and shorter treatment courses.

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Recommendation

43. In mechanically ventilated patients with COVID-19 and respiratory failure, we **suggest** using empiric antimicrobials/antibacterial agents, over no antimicrobials.

Weak recommendation, low-quality evidence.

Remark: if the treating team initiates empiric antimicrobials, they should assess for de-escalation daily, and re-evaluate the duration of therapy and spectrum of coverage based on the microbiology results and the patient's clinical status.

Rationale

There are no controlled clinical trials evaluating the use of empiric antimicrobials in COVID-19 patients or other coronaviruses. This recommendation is therefore based upon extrapolation of data from other viral pneumonias, particularly influenza [154]. Identifying bacterial coinfection or superinfection in patients with COVID-19 is challenging, as the symptoms may be similar to those of the underlying viral infection. The diagnostic difficulty is reflected in high rates of intravenous antibiotics administered in Wuhan: 53% with non-severe disease and > 90% of patients admitted to hospital or the ICU [1, 42, 43]. Data on the prevalence of bacterial superinfection in patients with COVID-19 are limited, as in larger case studies clinicians were often too overwhelmed to systematically obtain high-quality samples [1].

In critically ill patients with MERS, 18% had bacterial and 5% viral co-infections [155]. Co-infection with taphylococcus aureus is common with influenza pneumonia and can be especially virulent [154]. Recent clinical practice guidelines recommend initiating empiric antibacterial therapy in adults with community-acquired pneumonia who test positive for influenza [154]. Data

from critically ill patients demonstrate secondary infection in about 11% of cases, although the numbers are small. Isolated organisms included gram-negative organisms such as K. pneumoniae, P. aeruganosa, and S. marcescens. On the basis of these limited data it is difficult to determine patterns of superinfection, including the risk of S. aureus infection, commonly seen in influenza.

In patients with COVID-19 and hypoxic respiratory failure requiring mechanical ventilation, the panel suggest empiric antimicrobial treatment, on the basis that superinfection is reasonably common in this population and may to lead to a substantial increase in mortality, as in pandemic influenza [156–158]. Therefore, critically ill patients with suspected or confirmed COVID-19 should be treated with empiric antimicrobial therapy in accordance with the clinical syndrome (e.g. community-acquired or hospital- acquired pneumonia). Secondary infections occur in patients with COVID-19, but the incidence is unknown given the very limited data [159]. These infections should be treated according to clinical and microbiological data.

Referenzen:

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Recommendation

44. For critically ill adults with COVID-19 who develop fever, we ***suggest*** using acetaminophen/paracetamol for temperature control, over no treatment.

Weak recommendation, low-quality evidence.

Rationale

The majority of patients with COVID-19 develop fever during hospitalization (92% of those with severe disease). In the largest report from China, the median temperature across 1099 patients was 38.3 °C (IQR 37.8–38.9) [1]. Data from critically ill patients in general are available. We reviewed the literature and identified 12 RCTs (1785 patients) that examined the effect of fever control in the critically ill population, excluding neurological indication for temperature control [160–171]; active temperature management (pharmacologic or non-pharmacologic) did not reduce the risk of death (RR 1.03, 95% CI 0.81–1.31), ICU length of stay (MD − 0.07 days, 95% CI − 0.70– 0.56), but it was effective in reducing body temperature (MD − 0.36 °C, 95% CI − 0.42 lower to − 0.29). Given the safety of acetaminophen and lack of harm in the body of evidence, increasing patient comfort through fever management maybe important. Therefore, we issued a suggestion for clinicians to consider using pharmacologic agents for controlling fever in COIVD-19 patients.

The use of non-steroidal anti-inflammatory drugs to treat fever in patients with COVID-19 continues to be debated. Until more evidence is available, we suggest using acetaminophen/paracetamol to treat fever.

Referenzen:
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Recommendation

45. In critically ill adults with COVID-19, we **suggest against** the routine use of standard intravenous immunoglobulins (IVIG).

Weak recommendation, low-quality evidence.

Rationale

The use of intravenous immunoglobulin (IVIG) has been reported in several series of COVID-19 patients, but no efficacy data are available [172]. In the absence of adequate titers of neutralizing antibodies, standard intravenous immunoglobulin is unlikely to have a biologic effect in COVID-19. While IVIG may have immunomodulatory actions, its use can, rarely, also be associated with an increased risk of serious adverse events including anaphylactic reactions, aseptic meningitis, renal failure, thromboembolism, hemolytic reactions, transfusion-related lung injury, and other late reactions [173]. Preparations of anti-SARS-CoV-2 polyclonal or monoclonal antibodies are being developed. However, data from recent trials on the use of antibody-based therapies (immune plasma, hyperimmune globulin, monoclonal antibody to hemagglutinin stalk [173] in hospitalized seasonal influenza patients did not demonstrate improvement in outcomes [174–176].

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Recommendation

46. In critically ill adults with COVID-19, we **suggest against** the routine use of convalescent plasma.

Weak recommendation, low-quality evidence

Rationale

Convalescent plasma obtained from patients who have recovered from COVID-19 has been suggested as a potential therapy that may provide passive immunity from SARS-CoV2-specific antibodies [177]. Convalescent plasma has been used to treat several other viral infections, including those caused by SARS coronavirus, avian influenza A (H5N1) virus, and influenza A (H1N1) pdm09 virus [178–182]. A recent meta-analysis of observational studies using passive

immunotherapy for the treatment of severe acute respiratory infections of viral etiology suggests that convalescent plasma therapy was associated with reduction in mortality (OR 0.25, 95% CI 0.14–0.45) [183]. During the current outbreak in China, convalescent plasma was used in some patients with COVID-19 [184]. However, data on the efficacy and safety of convalescent plasma are limited, and the target for sufficient levels of neutralizing antibody titers against SARS-CoV-2 is unknown. A study on MERS concluded that use of convalescent plasma might be feasible but was challenging due to a small pool of potential donors with sufficiently high antibody titers [185]. An RCT in patients with confirmed Ebola virus disease showed that convalescent plasma, with unknown levels of neutralizing antibodies, was not associated with improvement in survival [186]. Another RCT in patients with seasonal influenza treated with high-titer versus low-titer anti-influenza immune plasma was terminated for futility because of the lack of effect on the primary outcome measured by a 6-point ordinal scale of clinical status on Day 7 [187]. Given the lack of convincing evidence from RCTs and the uncertainty surrounding the optimal preparation of convalescent plasma and its safety, we suggest that it should not be routinely used in treating patients with COVID-19 until more evidence is available.

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Recommendation

47. In critically ill adults with COVID-19:

47.1. We **suggest against** the routine use of lopinavir/ritonavir (*weak recommendation, low-quality evidence*).

47.2. **There is insufficient evidence to issue a recommendation** on the use of other antiviral agents in critically ill adults with COVID-19.

Rationale

The prolonged detection of SARS-CoV-2 RNA in the respiratory tract and sometimes other sites of seriously ill COVID-19 patients provides the rationale for administration of antiviral agents to reduce replication in efforts to improve clinical outcomes [45]. At present, no direct-acting antivirals have been proven to inhibit replication or provide clinical benefit in COVID-19 or MERS patients. A considerable number of agents approved for other indications have been proposed for use, but the comments below address the most promising ones. Several others are undergoing testing (e.g. arbidol [umifenovir], favipiravir, ribavirin, traditional Chinese medicines, inhaled interferons), alone or in combinations, and in one or more countries. Lopinavir is an antiretroviral protease inhibitor used in combination with ritonavir to ensure adequate lopinavir exposure for the treatment of human immunodeficiency virus (HIV) infection [188]. Because it was found to show in vitro activity against SARS-CoV, lopinavir/ritonavir was administered, in combination with high-dose oral ribavirin and a tapering course of systemic corticosteroids, in a cohort of 41 patients with SARS, and was found to be associated with significantly fewer adverse clinical outcomes (ARDS or death) compared with ribavirin alone used in 111 historical controls that received ribavirin and corticosteroids [189]. In a high-throughput screening for antiviral compounds, lopinavir inhibited replication of MERS-CoV in vitro [190]. In an animal model of MERSCoV infection, treatment with lopinavir/ritonavir or IFN-β1b was associated with virologic, histologic and clinical improvement versus placebo [191]. Lopinavir/ritonavir in combination with interferon beta 1-b is being tested in an RCT in MERS-CoV patients [192]. This combination was considered the second candidate in a WHO research prioritization list of therapeutic agents [193]. The drug has a generally good safety profile, but may have interactions with many drugs commonly used in critically ill patients (http://www.covid19-druginteractions.org/).

A recent RCT compared the use of lopinavir/ritonavir to usual care in 199 hospitalized patients with COVID-19 in China [194]. In this trial, lopinavir/ritonavir did not significantly reduce 28-day mortality (RD − 5.8%; 95% I − 17.3 to 5.7) or time to clinical improvement (MD 1.31 days, 95% CI 0.95–1.80). In addition, lopinavir/ritonavir was associated with more adverse events [194]. This trial is the only available direct evidence on the use of lopinavir/ritonavir in patients with COVID-19, however, it has several limitations. The trial was unblinded and it enrolled a small number of patients (n = 199) with a small number of events (44 deaths in total), which limits our confidence in its results. Nevertheless, the routine use of

lopinavir/ritonavir in critically ill patients is probably not warranted, and a weak recommendation against the routine use of lopinavir/ritonavir in critically ill COVID-19 patients is reasonable.

Lopinavir/ritonavir is one of the arms in a planned WHO core treatment protocol for hospitalized patients with COVID-19, and in the REMAP-CAP (Randomized, Embedded, Multifactorial Adaptive Platform Trial for Community-Acquired Pneumonia) trial (NCT02735707) The results of ongoing trials will help increase the precision of estimates and the certainty in the evidence. Remdesivir is the prodrug of an adenosine analog, which incorporates into nascent viral RNA chains and results in premature termination. It was considered the most promising drug in an informal consultation on research prioritization of candidate therapeutic agents by WHO [195]. Currently, there are published case reports but no published trials on the use of remdesivir in COVID-19. Remdesivir demonstrated effective inhibition of SARS-CoV-2, MERS-CoV, and SARS-CoV in in vitrostudies [196]. Furthermore, studies in animal models of MERS-CoV showed that it was more effective than control and superior to lopinavir/ritonavir combined with systemic IFN-β [197, 198]. Although intravenous remdesivir appears to adequately tolerated, a recent RCT showed that it was less effective than several antibody therapies in Ebola virus disease [199]. There are several ongoing RCTs that aim to examine the efficacy and safety of intravenous remdesivir for severe COVID-19 (clinicaltrials. gov NCT04257656) and for mild and moderate COVID-19 (clinicaltrials.gov NCT04252664). Another trial sponsored by the National Institute of Allergy and Infectious Diseases is recruiting patients in USA (clinicaltrials. gov NCT04280705). We will update our guidelines as new evidence emerges.

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Recommendation

48. **There is insufficient evidence to issue a recommendation** on the use of recombinant rIFNs, alone or in combination with antivirals, in critically ill adults with COVID-19.

Rationale

Recombinant interferon, often combined with ribavirin therapy, has been used in patients with MERS and SARS [179, 200–202]. Different preparations of recombinant rIFNs (rIFN-α2a, rIFN-α2b, rIFN-β1a and rIFN-β1b) have shown activity against MERS-CoV in Vero and LLCMK2 cells, and in a rhesus macaque model of MERS-CoV infection [200, 201, 203]. The largest cohort of critically ill patients with MERS showed that rIFN-α2a, rIFN-α2b, rIFN-β1a and ribavirin were not associated with lower mortality (OR 1.03, 95% CI .73–1.44) or reduced viral clearance when adjusted for time-varying covariables [204]. The relative effectiveness of different interferons against SARS-CoV-2 is unknown at this point. In vitro data showed that rIFN-β displayed the strongest MERS-CoV inhibition among different rIFN preparations (rIFN-α2b, rIFN-γ, rIFN-universal, and rIFN-α2a, rIFN-β), at 41 times lower than the previously reported 50% inhibitory concentration (IC50) of rIFN-α2b [203, 205]. An RCT to examine the effect of a combination of lopinavir/ritonavir and rIFN-β-1b on mortality of hospitalized patients with MERS is currently recruiting patients [206]. Unpublished data indicate that IFN-β inhibits SARS-C0V-2 in cell culture, and IFNs have been prioritized for study in COVID-19 by the WHO.

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Recommendation

49. **There is insufficient evidence to issue a recommendation** on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19.

Rationale

Chloroquine and its metabolite, hydroxychloroquine, are antimalarial agents that have demonstrated antiviral effects on SARS-CoV and SARS-CoV-2 in vitro [196, 207, 208]. Prior studies found inhibitory effects of chloroquine for multiple RNA viruses in vitro, but RCTs in treatment of dengue and chikungunya virus infections and of influenza prophylaxis failed to demonstrate antiviral or clinical benefits [209]. In one non-human primate model of chikungunya infection, it was shown that chloroquine's immunomodulatory effects were associated with delayed immune responses, higher levels of viral replication, and worse illness [210]. A news briefing suggested that its use in more than 100 patients showed "that it was superior to the control in inhibiting the exacerbation of pneumonia, improving lung imaging findings, promoting a virus negative conversion, and shortening the disease course", but the data have not been published yet [211]. A recent consensus document recommended chloroquine phosphate 500 mg twice daily for minimum of 5 days, with dose modifications if severe gastrointestinal side effects occur [212]. Since chloroquine is not available in some countries, hydroxychloroquine is an alternative. A recent study in China explored various dosing regimens of chloroquine and hydroxychloroquine using physiologicallybased pharmacokinetic models [208]. The study found hydroxychloroquine to be more potent than chloroquine in inhibiting SARS-CoV-2 in vitro. Based on these models, a hydroxychloroquine loading dose of 400 mg twice daily followed by 200 mg twice daily for 4 days was recommended [208]. A recent systematic review found no published studies in COVID-19 patients [213]. Pending the results of ongoing trials, we were unable to issue a recommendation for or against chloroquine.

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Recommendation

50. **There is insufficient evidence to issue a recommendation** on the use of tocilizumab in critically ill adults with COVID-19.

Rationale

Tocilizumab is a humanized immunoglobulin that functions in the immune response and blocks IL-6 receptor binding to IL-6. It has been approved for CRS and other inflammatory conditions related to IL-6 related inflammation, such as rheumatoid arthritis and juvenile idiopathic arthritis [214–217]. Severely ill patients with COVID-19 may have an extreme immune response leading

to severe respiratory failure. In such cases, inhibition of IL-6 may help attenuate the cytokine release syndrome by reducing cytokine concentrations and acute phase reactant production [218]. Ongoing trials of tocilizumab will help address the safety and efficacy of this therapy in COVID-19.

From the rheumatoid arthritis literature, a systematic review and meta-analysis of 6 RCTs (3 with 8/mg dose and 3 with 4 mg/kg dose) showed an increased risk of adverse events compared with control treatment (OR 1.53, 95% CI 1.26–1.86), and an increased risk of infections (OR 1.30, 95% CI 1.07–1.58) [219]. Another systematic review and meta-analysis of RCTs on tocilizumab in rheumatoid arthritis found an increased risk of infectious respiratory adverse events (RR 1.53, 95% CI 1.04–2.25) [220]. Since we have no data on the safety or efficacy of tocilizumab in COVID-19, we were unable to issue a recommendation.

Other agents

Nafamostat is a synthetic serine protease inhibitor and a potent inhibitor of MERS CoV. Nitazoxanide is an antiprotozoal agent with antiviral potential against several respiratory viruses including influenza, parainfluenza, respiratory syncytial virus, and rhinovirus. An in vitro study showed that both nafamostat and nitazoxanide inhibited SARS-CoV-2 [196]. An RCT in patients with acute uncomplicated influenza demonstrated that the use of nitazoxanide reduced the duration of symptoms [221]. However, in hospitalized patients with severe acute respiratory infection in Mexico, nitazoxanide was not found to be superior to placebo [222].

Referenzen:
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218. Chen X, et al. (2020) Detectable serum SARS-CoV-2 viral load (RNAaemia) is closely associated with drastically elevated interleukin 6 (IL-6) level in critically ill COVID-19 patients. medRxiv: 2020.2002.2029.20029520
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Ye Z et al., 2020 [12].

Treatment of patients with nonsevere and severe coronavirus disease 2019: an evidencebased guideline

Zielsetzung/Fragestellung

We have developed an evidence-based guideline that focuses on both patients with nonsevere and severe COVID- 19 and, for use of corticosteroids, patients with ARDS.

Methodik

Grundlage der Leitlinie

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

Recherche/Suchzeitraum:

- searches on MEDLINE, Embase, PubMed, Cochrane Central Register of Controlled Trials and medRxiv in March 2020 and applied no restriction on the language of publication.
- We also updated the direct evidence from COVID-19 to Apr. 25, 2020.

LoE/GoR

- To assess risk of bias in RCTs, we used a modified version of the Cochrane 1.0 risk of bias instrument. To assess risk of bias in cohort and case–control studies, we used instruments developed by the CLARITY (Clinical Advances through Research and Information Translation) research group at McMaster University, Hamilton, Ontario
- Grading of Recommendations Assessment, Development and Evaluation (GRADE)

Sonstige methodische Hinweise

- Because we anticipated a paucity of direct evidence from studies of patients with COVID-19, we summarized related indirect evidence from patients with SARS, MERS, ARDS, influenza, communityacquired pneumonia and, for adverse effects of convalescent plasma, Ebola virus disease. Using the GRADE approach, for efficacy outcomes from patients with SARS or MERS, we rated the evidence down 1 category for indirectness; for efficacy evidence from ARDS, influenza, community-acquired pneumonia and other acute viral infectious diseases, we rated the evidence down 2 categories for very indirect evidence. The panel considered evidence regarding adverse effects as less indirect than efficacy evidence and so rated the evidence down only once, or in some cases not at all, for indirect evidence.
- Definition of severe COVID-19 pneumonia follows that of the WHO: fever or suspected respiratory infection, plus 1 of the following: respiratory rate > 30 breaths/min, severe respiratory distress, or arterial oxygen saturation measured by pulse oximeter (SpO2) ≤ 93% on room air.8 The WHO definition of “severe” includes patients admitted to hospital with pneumonia who can be managed on medical wards and are not critically ill. Best evidence suggests that about 85% of such patients will never progress to critical illness such as ARDS.1
- Because we anticipate that clinicians are unlikely to consider the use of convalescent plasma in patients with nonsevere COVID-19, for this intervention we addressed only patients with severe COVID-19. Similarly, clinicians are unlikely to consider corticosteroids in patients with nonsevere infection; in addressing corticosteroids use, we therefore focused on patients with severe COVID-19 and those with ARDS.
- At the time we determined the scope of the guideline, we decided not to include remdesivir because it was not licensed for use anywhere in the world and tocilizumab because there were no studies available regarding its use. Both drugs are now among those being considered for use in COVID-19 and our failure to address them constitutes a limitation of this guideline.

Recommendations:

Corticosteroids

Empfehlung 1:

We suggest using corticosteroids in patients with severe coronavirus disease 2019 (COVID-19) and acute respiratory distress syndrome (ARDS) (weak recommendation).

Comment: The agent, dose and duration of corticosteroid varied in the relevant randomized controlled trials (RCTs). Methylprednisolone 40 mg intravenously for 10 days represents 1 reasonable regimen used by critical care clinicians on our panel.

Direct evidence

In 1 observational study[3] of patients with severe COVID-19 and ARDS, the administration of methylprednisolone reduced the risk of death (adjusted hazard ratio [HR] 0.41, 95% confidence interval [CI] 0.20 to 0.83; very low-quality evidence) (Appendix 1, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[9]

Indirect evidence

The biological rationale for administering corticosteroids in a variety of conditions causing ARDS — including viral infections, bacterial infections and noninfectious causes — is similar and relates to the effect of corticosteroids on the inflammatory cascade and subsequent alveolitis leading to respiratory compromise. Evidence from 851 patients with ARDS in 7 RCTs suggests

that use of corticosteroids results in a reduction in mortality that, applied to patients with COVID-19, may reduce deaths by 17.3% (95% CI –27.8% to –4.3%; low-quality evidence) (Appendix 1).[9]

Corticosteroids may reduce the duration of mechanical ventilation by more than 4 days (low-quality evidence), but we are very uncertain regarding the effect of corticosteroids on length of stay in the intensive care unit (ICU) and length of hospital stay (Appendix 1).[9]

Corticosteroids may increase serious hyperglycemia events by 8.1% (low-quality evidence), may have little or no effect on gastrointestinal bleeding and neuromuscular weakness (lowquality evidence), and probably have little or no effect on superinfection (moderate-quality evidence) (Appendix 1).[9]

Rationale

Use of corticosteroids in patients with severe COVID-19 and ARDS may result in a substantial reduction in mortality, a critical outcome. The harm of short-term use of corticosteroids is limited. Based on our inferences regarding patients' values and preferences, we made a weak recommendation in favour of corticosteroids.

Referenzen:
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Empfehlung 2:

We suggest not using corticosteroids in patients with severe COVID- 19 who do not have ARDS (weak recommendation).

Comment: If clinicians choose to use corticosteroids in patients who do not have ARDS, lower doses of corticosteroids for short periods may reduce the likelihood of toxicity.

Direct evidence

Very low-quality evidence from 2 cohort studies[10,11] that included 331 patients with severe COVID-19 raised the possibility that corticosteroids may increase mortality compared with no corticosteroids (HR 2.30, 95% CI 1.00 to 5.29); 1 of these studies[11] is a preprint (Appendix 1).[9]

Indirect evidence

Very low-quality evidence from 6129 patients with severe acuterespiratory syndrome (SARS) in 2 observational studies[12,13] raises the possibility that corticosteroids may reduce mortality. Evidence from 290 patients with Middle East respiratory syndrome (MERS) in 1 observational study[14] also suggests that corticosteroids may reduce mortality, but again the evidence is very low quality. Evidence from SARS and MERS provides very low-quality evidence that corticosteroids may delay clearance of coronavirus ribonucleic acid (RNA) (Appendix 1).[9] Efforts should be made to study corticosteroids for viral pneumonia (as distinct from ARDS) in RCTs.

Very low-quality evidence from 8530 patients with influenza in 11 observational studies raises the possibility that corticosteroids may increase mortality. It remains possible that corticosteroids increase superinfection and the need for mechanical ventilation (very low-quality evidence) (Appendix 1).[9]

Very low-quality evidence from 2034 patients with communityacquired pneumonia in 13 RCTs raises the possibility that corticosteroids may reduce mortality. Corticosteroids may reduce the need for mechanical ventilation by 10.4% (95% CI –13.8% to –4.3%; low-quality evidence), while very low-quality evidence raises the possibility of reductions in length of ICU stay, length of hospital stay and duration of mechanical ventilation. Corticosteroids probably increase serious hyperglycemia events by 5.7% (0.18% to 15.3%; low-quality evidence) and may increase neuropsychiatric events and

superinfection events (low-quality evidence). Corticosteroids may have little or no effect on gastrointestinal bleeding (low-quality evidence) (Appendix 1).[9]

Rationale

In patients with severe COVID-19 outside the ICU, any benefit of corticosteroids is less than in those with ARDS. The indirect evidence regarding mortality was very low quality and inconsistent among SARS, MERS, influenza and community-acquired pneumonia. Lowquality evidence suggests that corticosteroids, when used over the short term, have modest harm. In this context, when any benefit is very uncertain, our inferences regarding patient values and preferences dictate a weak recommendation against use of corticosteroids in patients with severe COVID-19 who do not have ARDS.

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Convalescent plasma

Empfehlung 3:

We suggest not using convalescent plasma in patients with severe COVID-19 (weak recommendation).

Indirect evidence

Very low-quality evidence from 40 patients with SARS in 1 observational study[15] raises the possibility that convalescent plasma may reduce mortality (Appendix 2, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[16] Four RCTs[17–20] that included 572 patients with influenza contributed to very low-quality evidence suggesting that convalescent plasma may have little to no effect on mortality, may have a small benefit in hastening recovery and may reduce length of hospital stay and duration of mechanical ventilation. Use of convalescent plasma may result in little or no difference in rate of serious adverse events (–1.2%, 95% CI –3.5% to 2.3%; low-quality evidence) (Appendix 2).[16]

Rationale

Very low-quality evidence raised the possibility that convalescent plasma may have some benefit in important outcomes and may be safe. Given the resources associated with preparation and administration of convalescent plasma, we have insufficient evidence to support its use.

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Antiviral drugs

Empfehlung 4:

We suggest not using ribavirin, umifenovir, favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with nonsevere COVID-19 (weak recommendation).

Because the likelihood of death from COVID-19 in patients with nonsevere disease is extremely low (in the range of 1/1000), we are very confident that antiviral drugs will have little or no effect on mortality in such patients.[1]

An RCT[21] of umifenovir and lopinavir-ritonavir reported other relevant outcomes in patients with nonsevere COVID-19, including cough, fever and progression to severe disease, but the RCT included only a total of 23 patients treated with umifenovir and 28 patients treated with lopinavir-ritonavir; as a result, the confidence intervals were so wide as to make the evidence uninformative (Appendix 3, available at www.cmaj.ca/lookup/suppl/doi:10.1503/cmaj.200648/-/DC1).[22] One observational study[23] in 120 patients with COVID-19 with mixed-severity disease provides very low-quality evidence that lopinavir-ritonavir may increase viral clearance at day 23 (Appendix 3).[22]

With respect to interferon-α, an observational study[24] in 70 patients with mixed-severity COVID-19 provides very low-quality evidence that the addition of interferon-α to umifenovir therapy may not affect time to viral clearance or length of hospital stay relative to umifenovir alone. There is no published evidence regarding benefit or harm of interferon-β or ribavirin in patients with nonsevere COVID-19.

With regard to favipiravir, an RCT[25] in 236 patients with mixedseverity COVID-19 suggested, in comparison with umifenovir, a possible higher incidence of recovery at day 7, but because of risk of bias, imprecision and indirectness, the evidence was only very low quality (Appendix 3).[22] One observational study[26] in 80 patients with nonsevere COVID-19 provides very low-quality evidence that favipiravir may increase viral clearance at day 7 relative to lopinavir-ritonavir. Symptomatic benefit outcomes from patients with nonsevere disease for other agents were unavailable.

Turning to harms, studies of interferon-α did not address symptomatic harms. Observational studies suggested substantial increases in anemia (26%) and bradycardia (15%) with ribavirin, but whether patients experienced symptoms remains uncertain.[27] Evidence regarding adverse effects in umifenovir is very low quality, and for favipiravir is low quality (Appendix 3)[22] An RCT[28] of lopinavirritonavir provides moderate-quality evidence of increased diarrhea (6%), nausea (9.5%) and vomiting (6.3%) with this drug combination.

Evidence for hydroxychloroquine came from 3 RCTs[29–31] of 40 patients with nonsevere COVID-19. Because of serious risk of bias (lack of blinding), imprecision (wide confidence intervals) and indirectness (both intervention and control groups included other drugs, limiting inferences regarding the effect of hydroxychloroquine), these studies provided very low-quality evidence regarding the following possible effects: little or no effect on viral clearance, a small reduction in duration of fever, little or no progression from nonsevere to severe disease, and little or no effect on recovery at day 7 (Appendix 3).[22] Hydroxychloroquine may cause diarrhea in about 10% of patients (low-quality evidence). Very low-quality evidence suggests possible increases in headache, rash, nausea, vomiting and blurred vision (Appendix 3).[22]

Rationale

Because of a very low incidence of death, antiviral drugs cannot result in important mortality reductions in patients with nonsevere disease. We have no persuasive evidence of symptomatic benefit for any drug, with evidence of appreciable harm with ribavirin and lopinavir-ritonavir and high uncertainty regarding adverse effects in other drugs. Efforts should be made to study these agents in RCTs.

For all drugs to this point, the panel reached a consensus. For hydroxychloroquine, there was no suggestion of benefit in patients with nonsevere COVID-19, with possible increases in rash, nausea and vomiting. For hydroxychloroquine, 15 panel members voted for a weak recommendation against the drug, 3 voted for no recommendation, and 7 members had intellectual competing interests and did not vote.

Referenzen:

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30. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020 Apr. 10. doi: 10.1101/2020.03.22.20040758.
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Empfehlung 5:

We suggest not using ribavirin, umifenovir, favipiravir, lopinavir-ritonavir, hydroxychloroquine, interferon-α and interferon-β in patients with severe COVID-19 (weak recommendation).

Indirect evidence

Observational studies[12,32–34] of ribavirin and interferon in non–COVID-19 coronaviruses (SARS and MERS) provide point estimates suggesting mortality reductions, but confidence intervals are very wide and include mortality increases; overall, the evidence is very low quality (Appendix 3).[22] As presented in the previous section, an observational study[27] suggests frequent anemia and bradycardia in patients receiving ribavirin, but the effect on patient experience remains uncertain.

Direct evidence

We have no direct evidence for ribavirin or interferon-β in severe COVID-19 disease. For interferon-α, as presented in the previous section, an observational study[24] provides very low-quality evidence that the drug has minimal or no effect on time to viral clearance or length of hospital stay.

For umifenovir, the only RCT[21] enrolled 23 patients with nonsevere COVID-19 disease, leaving (in addition to indirectness of evidence from patients with nonsevere disease) confidence intervals for all outcomes so wide as to be uninformative (Appendix 3).[22] An observational study[35] in 504 patients with mixed-severity COVID-19 provides very low-quality evidence that umifenovir may decrease mortality.

For favipiravir, we noted in the previous section the very lowquality evidence of increased viral clearance relative to lopinavirritonavir (Appendix 3). An RCT[36] of lopinavir-ritonavir in 386 patients with influenza suggests the drug may not cause diarrhea (the results of this RCT have not yet been published).

Evidence from 199 patients with severe COVID-19 in 1 RCT[28] suggests that lopinavir-ritonavir may reduce mortality by 2.4% (95% CI −5.7% to 3.1%), length of ICU stay by 5 days (95% CI −9 to 0), and length of hospital stay by 1 day (95% CI −2 to 0), but given the 95% confidence intervals, the results include the possibility of no effect (all low-quality evidence, from imprecision and risk of bias). We found moderate-quality evidence of increases in diarrhea (6%), nausea (9.5%) and vomiting (6.3%) for lopinavir-ritonavir (Appendix 3).[22] As presented in the previous section, 1 observational study[23] in 120 patients with mixed-severity COVID-19 provides very low-quality evidence that lopinavir-ritonavir may increase viral clearance at day 23 (Appendix 3).[22] Very low-quality evidence from 181 patients with severe COVID-19 and 255 patients with mixedseverity disease in 2 observational studies (preprints)[37,38] raised the possibility that hydroxychloroquine may increase mortality and the need for mechanical ventilation (Appendix 3).[22]

Rationale

Very low-quality evidence raised the possibility that ribavirin, umifenovir, favipiravir, interferon-α and interferon-β may have little or no benefit in mortality for patients with severe COVID-19. We are also very uncertain regarding the safety of these drugs in patients with severe disease. The panel reached consensus on all recommendations regarding antiviral drugs mentioned thus far. As described above, however, for lopinavir-ritonavir, although 1 RCT[28] suggested the combination may reduce mortality, the 95% CI (–5.7% to 3.1%) included a 3.1% increase in mortality, and because of an open-label design, the study was at high risk of bias. Similarly, the 95% CI with respect to estimates of decreased length of ICU and hospital stay included no effect, and the evidence was overall low quality. Considering the uncertainty and the likely increases in diarrhea (best estimate 6%), nausea (9.0%) and vomiting (6.4%), the panel made a weak recommendation against the use of lopinavir-ritonavir. Ultimately, 14 panel members voted to recommend against the drug combination, and 6 were in favour; 5 members had intellectual competing interests and did not vote.

In patients with severe COVID-19, 2 observational studies[37,38] raised the possibility that hydroxychloroquine may increase mortality and the need for mechanical ventilation. Ultimately, 15 panel members voted for a weak recommendation against the drug, 3 voted for no recommendation, and 7 members had intellectual competing interests and did not vote.

Referenzen:

12. Lau EHY, Cowling BJ, Muller MP, et al. Effectiveness of ribavirin and corticosteroids for severe acute respiratory syndrome. Am J Med 2009;122:1150.e11-21
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Infectious Diseases Society of America (IDSA), 2020 [6].

Infectious Diseases Society of America Guidelines on the Treatment and Management of Patients with COVID-19 (Version 2.1.0)

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

Recherche/Suchzeitraum:

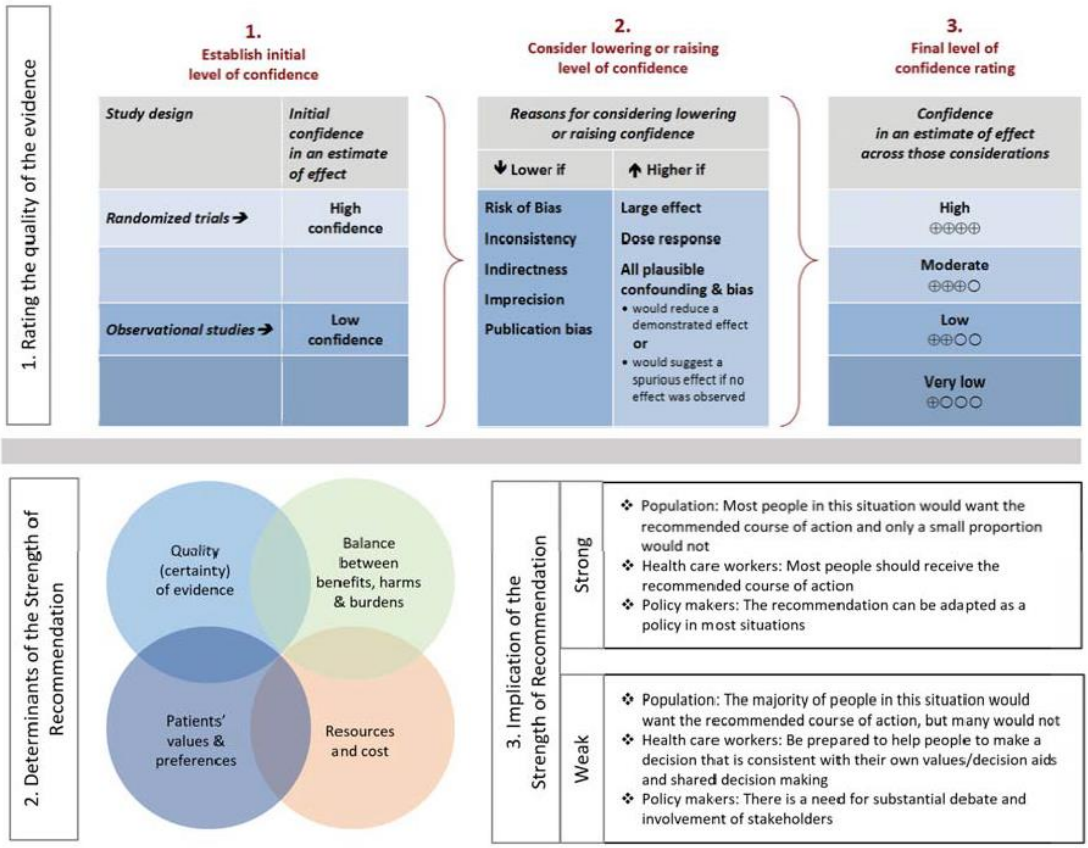
- Ovid Medline and Embase were searched from 2019 through June 18, 2020. Horizon scans have been performed regularly during the evidence assessment and recommendation process to locate additional grey literature and manuscript pre-prints. Reference lists and literature suggested by panelists were reviewed for inclusion. No restrictions were placed on language or study type.

LoE/GoR

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

their use and to avoid encouraging the rapid diffusion of potentially ineffective or harmful interventions.

Abbildung 3: 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.

Recommendation 1:

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

Recommendation 2:

Among patients with COVID-19, the IDSA guideline panel suggests against hydroxychloroquine/chloroquine plus azithromycin outside of the context of a clinical trial.

(Conditional recommendation, Very low certainty of evidence)

Summary of the evidence

Our search identified three RCTs and six comparative cohort studies of hospitalized patients with confirmed COVID-19 treated with HCQ reporting on mortality, clinical progression or clinical improvement, and adverse events [27-35] (Table s3a) (Table 1).

In addition, we identified three comparative cohort studies and one case-control study reporting adjusted analyses of hospitalized patients with confirmed COVID-19 treated with HCQ plus AZ reporting on the outcomes of mortality, failure of virologic clearance (assessed with polymerase chain reaction [PCR] test), and adverse events (i.e., significant QT prolongation leading to treatment discontinuation) [31, 33, 35, 36].

Benefits

Hydroxychloroquine

No mortality events were reported from 180 patients receiving either HCQ or no HCQ treatment across two RCTs [27, 29]. Five non-randomized studies failed to identify an association between persons treated with HCQ (compared to those not receiving HCQ) and mortality: Geleris 2020 reported an adjusted hazard ratio (HR) of 1.00 (95% confidence interval [CI]: 0.76, 1.32); Ip 2020 reported an adjusted HR of 1.02 (95% CI: 0.83, 1.27); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.99 (95% CI:0.50, 1.92); Mahévas 2020 reported a weighted HR of 1.20 (95% CI:0.40, 3.30); Rosenberg 2020 reported an adjusted HR of 1.08 (95% CI: 0.63, 1.85) [30-33, 35]. One non-randomized study reported a decrease in mortality among persons treated with HCQ (adjusted HR: 0.36, 95% CI: 0.18, 0.75) [34]. The currently available best evidence failed to demonstrate or to exclude a beneficial effect of HCQ on clinical progression of COVID-19 (as inferred by radiological findings; risk ratio [RR]: 0.61; 95% CI:0.26, 1.43) or on viral crearance by PCR tests (RR: 2.00; CI: 0.02, 20.00), although a somewhat higher proportion in the HCQ group experienced clinical improvement (RR: 1.47; 95% CI 1.02, 2.11). However, the certainty in the evidence was rated as very low mainly due to small sample sizes (sparse data), co-interventions, and risk of bias due to methodological limitations.

Hydroxychloroquine + Azithromycin

Three non-randomized studies failed to identify an association between treatment with HCQ + AZ and mortality: Ip reported an adjusted HR of 0.98 (95% CI: 0.75, 1.28); Magagnoli reported an adjusted HR in a subset after propensity score adjustment of 0.89 (95%CI: 0.45, 1.77); Rosenberg 2020 reported an adjusted HR of 1.35 (95% CI: 0.79, 2.40) [31, 33, 35].

Harms

Hydroxychloroquine

Four recent or ongoing RCTs did not show a harm signal among persons with or without COVID-19 receiving treatment with HCQ [37-40], as well as two larger observational studies [30, 33]. Across the body of evidence from three RCTs, treatment with HCQ may increase the risk of Experiencing adverse events (RR: 3.14, 95% CI: 1.58, 6,24, very low CoE); however, the evidence is uncertain [27-29]. Two non-randomized comparative studies suggest increased risk of QT prolongation among patients receiving HCQ compared to those not receiving HCQ (RR: 2.89, 95% CI 1,62, 5.16; very low CoE) [32, 33]. In addition, Rosenberg 2020 reported 166% of patients in the HCQ arm experienced arrhythmias compared with 10% in the non-HCQ arm (RR: 1.56; 95% CI: 0.97, 2.50).

Conclusions and research needs for this recommendation

The guideline panel recommends that, because of uncertainty regarding its risks and benefits, the use of HCQ should be only in the context of a clinical trial. Because of the potential for toxicity, the panel suggests aagainst HCQ+AZ combination outside of a clinical trial. This recommendation does not address the use of AZ for secondary bacterial pneumonia in patients with COVID-19. Additional RCTs and prospective outcome registries are needed to inform research for treatment with HCQ alone or in combination with AZ for patients with COVID-19

Referenzen:

27. Chen J, LIU D, LIU L, et al. A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Journal of Zhejiang University (Medical Sciences) 2020; 49(1): 0-.
28. Chen Z, Hu J, Zhang Z, et al. Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020. Last updated June 25, 2020 and posted online at www.idsociety.org/COVID19guidelines.
29. Tang W, Cao Z, Han M, et al. Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. bmj 2020;369.
30. Geleris J, Sun Y, Platt J, et al. Observational Study of Hydroxychloroquine in Hospitalized Patients with Covid-19. N Engl J Med 2020.
31. Magagnoli J, Narendran S, Pereira F, et al. Outcomes of hydroxychloroquine usage in United States veterans hospitalized with Covid-19. Med 2020.
32. Mahevas M, Tran V-T, Roumier M, et al. No evidence of clinical efficacy of hydroxychloroquine in patients hospitalized for COVID-19 infection with oxygen requirement: results of a study using routinely collected data to emulate a target trial. MedRxiv 2020.
33. Rosenberg ES, Dufort EM, Udo T, et al. Association of treatment with hydroxychloroquine or azithromycin with in-hospital mortality in patients with COVID-19 in New York state. Jama 2020.

Recommendation 3:

Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends the combination of lopinavir/ritonavir only in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

One RCT and two case studies reported on treatment with combination lopinavir/ritonavir for hospitalized patients with COVID-19 [56-58]. Cao et al. randomized 199 hospitalized patients with severe COVID-19 to receive treatment with lopinavir/ritonavir in addition to standard of care (n=99) or standard of care alone (n=100) for 14 days. The trial reported on the following outcomes: mortality, failure of clinical improvement (measured using a 7-point scale or hospital discharge), and adverse events leading to treatment discontinuation.

Benefits

Based on a modified intention to treat analysis, treatment with lopinavir/ritonavir failed to show or exclude a beneficial effect on mortality (RR: 0.67; 95% CI: 0.38, 1.17), although failure of clinical improvement was lower in the lopinavir group (RR: 0.78; 95% CI: 0.63, 0,97; ITT analysis).

Harms

Nearly 14% of lopinavir/ritonavir recipients were unable to complete the full 14-day course of administration due primarily to gastrointestinal adverse events, including anorexia, nausea, abdominal discomfort, or diarrhea, as well as two serious adverse episodes of acute gastritis. Two recipients also had self-limited skin eruptions. The risk of hepatic injury, pancreatitis, severe cutaneous eruptions, QT prolongation, and the potential for multiple drug interactions due to CYP3A inhibition, are all well documented with this drug combination.

Other considerations

The panel elected to inform their decision based on the RCT [58]. The panel determined the Certainty of evidence to be very low due to concerns with risk of bias (lack of blinding) and imprecision. In the randomized clinical trial conducted by Cao et al, the group that received lopinavir/ritonavir and the group that did not had similar rates of viral decay. This finding suggests that lopinavir/ritonavir is not having a measurable antiviral effect, its purported mechanism of action.

Conclusions and research needs for this recommendation

The guideline panel recommends the use of lopinavir/ritonavir only in the context of a clinical trial. Additional clinical trials or prospective outcome registries are needed to inform research for treatment with lopinavir/ritonavir and other HIV-1 protease inhibitors for patients with COVID-19.

Referenzen:
56. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv 2020.
57. Liu Y, Sun W, Li J, et al. Clinical features and progression of acute respiratory distress syndrome in coronavirus disease 2019. medRxiv 2020. Last updated June 25, 2020 and posted online at www.idsociety.org/COVID19guidelines.
58. Cao B, Wang Y, Wen D, et al. A Trial of Lopinavir-Ritonavir in Adults Hospitalized with Severe Covid-19. N Engl J Med 2020.

Recommendation 4:

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

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

Recommendation 5:

Among hospitalized patients with COVID-19 without hypoxemia requiring supplemental oxygen, the IDSA guideline panel suggests against the use of glucocorticoids.

(Conditional recommendation, Low certainty of evidence)

*Severe illness is defined as patients with percentage of oxyhemoglobin saturation (SpO_2) ≤ 94% on rrom air, and those who require supplemental oxygen, mechanical ventilation, or extracorporeal mechanical oxygenation (ECMO).

Summary of the evidence

Our search identified one RCT, one "partially" randomized trial, one prospective cohort, and five retrospective cohort studies [65-72]. The RCT provided the best available evidence on treatment with corticosteroids for persons with COVID-19 [65] (Tables 4 and 5). Corral-Gudino et al. reported on a study that randomized patients to receive methylprednisolone or standard of care; however, patients expressing a preference for methylprednisolone were assigned to the same treatment arm [66]. Corral- Gudino et al. did not report the disaggregated results from the randomized trial; therefore, succumbing to the same potential for bias as reported subsequently for the non-randomized studies. The non-randomized studies had significant limitations with controlling for multiple co-interventions and disease severity at baseline [67-72]. All non-randomized studies had concerns with risk of bias due to lack of adjustment for critical confounders or potential for residual confounding. Timing of receipt, dose and duration of corticosteroids varied across studies.

The RECOVERY trial is a randomized trial among hospitalized patients in the United Kingdom [65]. In that study, 2104 participants were randomized to receive dexamethasone (6 mg daily for up to 10 days) and 4321 were randomized to usual care. The RECOVERY trial reported on the outcomes of mortality and hospital discharge. Participants and study staff were not blinded to the treatment arms.

Benefits

Among hospitalized patients, 28-day mortality was 17% lower in the group that received dexamethasone than in the group that did not receive dexamethasone (RR 0.83; 0.74-0.92; Moderate certainty of evidence). In addition, at 28 days, patients receiving dexamethasone are more likely to be discharged from the hospital (RR: 1.11; 95% CI: 1.04, 1.19; Moderate certainty of evidence).

In sub-group analyses of patients without hypoxia not receiving supplemental oxygen, there was no evidence for benefit and a trend toward harm with dexamethasone in participants who were not on supplemental oxygen (RR 1.22; 0.86, 1.75; Low certainty of evidence).

Harms

Patients receiving a short course of steroids may experience hyperglycemia, neurological side effects (e.g., agitation/confusion), adrenal suppression, and risk of bacterial and fungal infection [67, 73, 74].

Other considerations

The panel agreed the overall certainty of evidence for treatment with glucocorticoids for patients with severe COVID-19 as moderate due to concerns with indirectness since the evidence was from dexamethasone. The panel agreed that the overall certainty of evidence for patients without hypoxemia requiring supplemental oxygen as low due to concerns with risk of bias (post hoc analysis) and imprecision.

Conclusions and research needs for this recommendation

The guideline panel suggests glucocorticoids for patients with severe COVID-19. The guideline panel suggests against glucocorticoids for patients with COVID-19 without hypoxemia requiring supplemental oxygen.

Additional research is needed to inform the generalizability of treatment with different glucocorticoids for patients with COVID-19.

Referenzen:
65. Horby P, Lim WS, Emberson J, et al. Effect of Dexamethasone in Hospitalized Patients with COVID-19: Preliminary Report. medRxiv 2020: 2020.06.22.20137273.
66. Corral L, Bahamonde A, Arnaiz delas Revillas F, et al. GLUCOCOVID: A controlled trial of methylprednisolone in adults hospitalized with COVID-19 pneumonia. medRxiv 2020: 2020.06.17.20133579.
67. Salton F, Confalonieri P, Santus P, et al. Prolonged low-dose methylprednisolone in patients with severe COVID-19 pneumonia. medRxiv 2020: 2020.06.17.20134031.
68. Wang Y, Jiang W, He Q, et al. Early, low-dose and short-term application of corticosteroid treatment in patients with severe COVID-19 pneumonia: single-center experience from Wuhan, China. medRxiv 2020: 2020.03.06.20032342.
69. Wu C, Chen X, Cai Y, et al. Risk Factors Associated With Acute Respiratory Distress Syndrome and Death in Patients With Coronavirus Disease 2019 Pneumonia in Wuhan, China. JAMA Intern Med 2020.
70. Fernandez-Cruz A, Ruiz-Antoran B, Munoz-Gomez A, et al. Impact of glucocorticoid treatment in SARS-CoV-2 infection mortality: a retrospective controlled cohort study. medRxiv 2020: 2020.05.22.20110544.
71. Lu X, Chen T, Wang Y, et al. Adjuvant corticosteroid therapy for critically ill patients with COVID-19. medRxiv 2020: 2020.04.07.20056390.
72. Yuan M, Xu X, Xia D, et al. Effects of Corticosteroid Treatment for Non-Severe COVID-19 Pneumonia: A Propensity Score-Based Analysis. Shock 2020.
73. Henzen C, Suter A, Lerch E, Urbinelli R, Schorno XH, Briner VA. Suppression and recovery of adrenal response after short-term, high-dose glucocorticoid treatment. Lancet 2000; 355(9203): 542-5.
74. Siemieniuk RA, Meade MO, Alonso-Coello P, et al. Corticosteroid Therapy for Patients Hospitalized With Community-Acquired Pneumonia: A Systematic Review and Metaanalysis. Ann Intern Med 2015; 163(7): 519-28.

Recommendation 6:

Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends tocilizumab only in the context of a clinical trial.

(Knowledge gap)

Summary of the evidence

Studies reporting on the pathogenesis of SARS-CoV-1 and MERS-CoV suggest a release of proinflammatory cytokines including interleukins-6 (IL-6) [75] during the clinical illness. Our search identified one study [75] that reported on 21 severe or critical patients with COVID-19 treated with tocilizumab, an IL-6 blocker (Table 6). This study had no control group. To estimate a control group rate in patients who did not get treatment with tocilizumab, Xu et al. described findings from Yang 2020, which suggested a baseline mortality rate of 60% in critical patients and 11% in severe patients admitted tot he ICU [76].

Benefits

We estimate that the patients in Xu 2020 (21 patients, 4 critical and 17 severe) would have a baseline mortality risk of 20% as matched in severity. Therfore, treatment with tocilizumab may have reduced mortality since there were no deaths reported out of 21 patients. However, this conclusion remains highly uncertain given the lack of a contemporaneous control or adjustments for confounding factors. Out of 21 patients, 19 were discharged from the hospital suggesting a 9.5% rate of clinical improvement in the CT scan findings.

Harms

Xu et al. reported no serious adverse events [75]. However, patients receiving tocilizumab are often at an increased risk of serious infections (bacterial, viral, invasive fungal infections, and tuberculosis) and hepatitis B reactivation [77]. Cases of anaphylaxis, severe allergic reactions, severe liver damage and hepatic failure, and intestinal perforation have been reported after tocilizumab administration in patients without COVID-19.

Tocilizumab is not metabolized by the cytochrome P450 isoenzyme system, however elevated IL-6 levels seen in inflammatory states have been shown to inhibit these enzymes, thereby slowing the metabolism of drugs through these pathways. As the 3A4 pathway is responsible for metabolism of many commonly used medications, administration of IL-6 inhibitors like tocilizumab may result in enhanced metabolism in drugs utilizing the cytochrome P450 system [78, 79].

Other considerations

The panel determined that the overall certainty of the evidence was very low due to concerns of high risk of bias due to confounding, indirectness, and imprecision.

Conclusions and research needs for this recommendation

The guideline panel recommended tocilizumab only in the context of a clinical trial. Additional clinical trials are needed to inform research on the effectiveness of treatment with tocilizumab for patients with COVID-19.

Referenzen:
75. Xu X, Han M, Li T, et al. Effective treatment of severe COVID-19 patients with Tocilizumab. ChinaXiv 2020; 202003(00026): v1.
76. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARSCoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. Lancet Respir Med 2020.
77. Genentech, Inc. ACTEMRA® (tocilizumab) injection, for intravenous or subcutaneous use. San Francisco, CA: Genentech, Inc., 2019.
78. Kim S, Ostor AJ, Nisar MK. Interleukin-6 and cytochrome-P450, reason for concern? Rheumatol Int 2012; 32(9): 2601-4.
79. Machavaram KK, Almond LM, Rostami-Hodjegan A, et al. A physiologically based pharmacokinetic modeling approach to predict disease-drug interactions: suppression of CYP3A by IL-6. Clin Pharmacol Ther 2013; 94(2): 260-8.

Recommendation 7:

Among patients who have been admitted to the hospital with COVID-19, the IDSA guideline panel recommends COVID-19 convalescent plasma only in the context of a clinical trial. (Knowledge gap)

Summary of the evidence

Our search identified one RCT and two comparative cohort studies, as well as one large (n=5000), single-arm registry study among hospitalized patients with COVID-19 receiving COVID-19 CP reporting on the outcomes of mortality, worsening oxygenation, and transfusion-related adverse events [87-90] (Table 7) (Tables3f). We identified an additional small (n=25) single-arm study; however, we excluded it because it did not provide the best available evidence and may have been included in the registry study [86].

All studies had concerns with risk of bias due to lack of adjustment for critical confounders or potential for residual confounding. Timing of receipt of COVID-19 CP during the clinical course of the patients' illness varied across studies.

Li 2020 randomized 103 patients to receive a transfusion or not in an open-label trial with more Than 90% of patents enrolled 14 days after symptom onset (median 30 days). Subjects were propensity score matched on the administration of HCQ and AZ, intubation status and duration, length of hospital stay, and oxygen requirement on the day of transfusion; however, there may have been some residual confounding. Duan 2020 compared 10 CP treated patients to 10 historical control patients matched on age, gender, and severity of illness; however, the study did not adjust for critical confounders including co-treatments, baseline characteristics, disease severity, and timing of plasma delivery. Joyner et al. 2020

reported on 5,000 patients with severe or life-threatening COVID-19 enrolled in the U.S. FDA Expanded Access Program for COVID-19 CP study and found <1% severe adverse events within the first four hours after administration.

Benefits

Convalescent plasma transfusion failed to show or to exclude a beneficial or detrimental effect on mortality; the evidence from both RCT and non-randomized studies is uncertain 8RR:0.65; 95%CI: 0.29, 1.47; very low CoE and HR: 0.34; 95%CI: 0.13, 0.89; very low CoE, respectively). Similarly, receipt of COVID-19 CP may reduce the odds of worsening oxygenation (adjusted odds ratio [OR]: 0.86;95%CI: 0.75,0.98; very low CoE; however, the evidence is uncertain because of concerns with risk of bias.

Harms

In the largest safety study, there were 15 deaths reported within 4 hours of transfusion in 5,000 patients (0.3%) [90] and four (0.08%) were judged as possibly related tot he transfusion of COVID-19 CP. In addition, 21 serious non-fatal adverse eventse (SAEs) were reported (0.4%): seven cases of transfusion-associated circulatory overload (TACO), 11 cases of transfusion-related acute lung injury (TRALI), and three cases of severe allergic transfusion reactions. Study authors judged all incidences of TACO and TRALI as related to the transfusion of COVID-19 CP. In another smaller study of 52 patients randomized to receive CP transfusions, two subjects developed transfusion-related adverse events (e.g., chills and rash; shortness of breath, cyanosis, and severe dyspnea) within 6 hours of receipt [87].

Other considerations

The panel agreed on the overall certainty of evidence as very low due to concerns with risk of bias and imprecision.

Conclusions and research needs for this recommendation

The guideline panel recommends COVID-19 CP only in the context of a clinical trial. Additional clinical trials are needed to inform benefit of treatment with COVID-19 CP for patients with COVID-19.

Referenzen:
86. Salazar E, Kuchipudi SV, Christensen PA, et al. Relationship between Anti-Spike Protein Antibody Titers and SARS-CoV-2 In Vitro Virus Neutralization in Convalescent Plasma. bioRxiv 2020.
87. Li L, Zhang W, Hu Y, et al. Effect of Convalescent Plasma Therapy on Time to Clinical Improvement in Patients With Severe and Life-threatening COVID-19: A Randomized Clinical Trial. JAMA 2020.
88. Liu ST, Lin H-M, Baine I, et al. Convalescent plasma treatment of severe COVID-19: A matched control study. medRxiv 2020.
89. Duan K, Liu B, Li C, et al. Effectiveness of convalescent plasma therapy in severe COVID-19 patients. Proc Natl Acad Sci U S A 2020; 117(17): 9490-6.
90. Joyner M, Wright RS, Fairweather D, et al. Early Safety Indicators of COVID-19 Convalescent Plasma in 5,000 Patients. medRxiv 2020.

Recommendation 8:

Among hospitalized patients with severe* COVID-19, the IDSA panel suggests remdesivir over no antiviral treatment (conditional recommendation, moderate certainty of evidence)

- Remark: For consideration in contingencyy or crisis capacity settings (i.e. limited remdesivir supply): Remdesivir appears to demonstrate the most benefit in those with severe COVID-19 on supplemental oxygen rather than in patients on mechanical ventilation or ECMO.

Recommendation 9:

Among patients with severe COVID-19 on supplemental oxygen but not on mechanical ventilation or ECMO, the IDSA panel suggests treatment with five days of remdesivir rather than 10 days of remdesivir. (Conditional recommendation, Low certainty of evidence)

- Remark: In patients on mechanical ventilation or ECMO, the duration of treatment is 10 days.

*Severe illness is defined as patients with $SpO_2 \leq 94\%$ on room air, and those who require supplemental oxygen, mechanical ventilation, or ECMO.

Summary of the evidence

Two RCTs comparing treatment with remdesivir (200 mg day one, 100 mg daily days 2-10) against no remdesivir treatment [96, 97], and one RCT comparing 5 days of treatment (200 mg day one, 100 mg daily days 2-5) against 10 days (200 mg day one, 100 mg daily days 2-10) of treatment [98] served as the best available evidence among hospitalized persons with severe COVID-19. The outcomes assessed were mortality, time to clinical improvement at 14 days, serious adverse events, and adverse events leading to treatment discontinuation.

The study by Wang et al 2020 was stopped early due to lack of recruitment into the trial due to decreased incidence in China. When comparing treatment with remdesivir to no remdesivir treatment data after 28-days of observation, we did

not pool the mortality data from the Wang et al study and 14-day mortality from the Beigel et al study (i.e., Adaptive Covid-19 Treatment Trial [ACTT-1]). This is because the preliminary analysis of the ACTT-1 presented the mortality results appropriately as time-to-event analysis due to possible chance effects at 14 days, as many patients still remained hospitalized, with 28-day mortality data still unavailable at the time of the preliminary analysis. Randomization performed in Goldman 2020 failed to establish prognostic balance between baseline clinical status among the 397 patients randomized into the treatment arms, with patients in the 10-day arm more severely ill at study entry. Even with the adjusted analysis, residual confounding is possible. In addition, participants, healthcare workers, and outcome assessors were not blinded to the treatment arms.

Benefits

Preliminary evidence in ACTT-1 showed a trend in reduction of mortality by remdesivir over no remdesivir treatment at 14 days (HR: 0.70; 95% CI: 0.47, 1.04; Moderate CoE) [96]. Wang et al. failed to show a mortality benefit at 28 days (RR: 1.09; 95% CI: 0.54, 2.18; Low CoE) [97] but, because the trial was stopped early, the study may have been under-powered to detect an effect. Patients receiving treatment with remdesivir may have greater clinical improvement at 28 days than patients not receiving remdesivir (RR: 1.13; 95% CI: 0.91, 1.41; Low CoE [97]. In addition, patients receiving treatment with remdesivir had a shorter median time to recovery (median 11 vs. 15 days; HR: 1.32; 95% CI: 1.12, 1.55; High certainty of evidence) [96].

In another study by Goldman et al that compared 5 and 10 days of treatment, the shorter course of remdesivir showed a trend toward decreased mortality (RR: 0.75; 95% CI: 0.51, 1.12; low CoE) and increased clinical improvement at 14 days (RR: 1.19; 95% CI: 1.01, 1.40; Low CoE); however, the evidence is uncertain because the persons in the 10-day group had more severe disease at baseline and there is the possibility of residual confounding despite the adjusted analysis [98].

Harms

Patients treated with remdesivir do not appear to experience greater SAEs (grade 3/4) than than those not receiving remdesivir (RR: 0.88; 95% CI: 0.74, 1.06; Moderate CoE) [96, 97].

Patients receiving five days of remdesivir may experience fewer SAEs and AEs leading to treatment discontinuation than patients receiving 10 days of remdesivir (RR: 0.61; 0.44, 0.85; Low CoE and RR: 0.44; 95% CI: 0.21, 0.95; Low CoE, respectively); however, this evidence is uncertain because of the increased severity of disease among patients in the 10 day arm [98].

Other considerations

The panel agreed that the overall certainty of the evidence for treatment with remdesivir compared to no remdesivir treatment was moderate due to concerns with imprecision. The panel decided to not pool the outcome of mortality as dichotomous data until 28-day data would be released from both trials, due to concerns with 14-day mortality showing a spurious effect. Given the limited evidence across baseline severity, the panel recognized a knowledge gap when assessing whether greater benefit could be attained for patients with less severe disease; however, the panel agreed that the reported data supported the prioritization of remdesivir among persons with severe but not critical COVID-19.

The panel agreed on the overall certainty of the evidence for treatment with a 5-day course compared to a 10-day course of treatment as low due to concerns with risk of bias and imprecision. The panel recognized the benefit of a shorter course of treatment, if providing similar or greater efficacy, on the availability of remdesivir.

Conclusions and research needs for this recommendation

The guideline panel suggests remdesivir rather than no remdesivir for treatment of severe COVID-19 in hospitalized patients. Additional clinical trials are needed to provide increased certainty about the potential for both benefit and harms of treatment with remdesivir, as well as understand the benefit of treatment based on disease severity.

Beigel 2020 reported that the 28-day follow up of the ACTT-1 will be made available. At that time, the outcomes will be reassessed.

Referenzen:
96. Beigel JH, Tomashek KM, Dodd LE, et al. Remdesivir for the Treatment of Covid-19 - Preliminary Report. N Engl J Med 2020.
97. Wang Y, Zhang D, Du G, et al. Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020; 395(10236): 1569-78.

Recommendation 10:

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

Summary of the evidence

Our search identified one cohort study that compared 84 patients treated with famotidine against 1,536 patients not receiving treatment with famotidine [101]. Fifteen percent of patients in the famotidine group (13/84) started famotidine at home before presenting to the hospital. In addition, a subset of 420 patients not treated with famotidine were matched on baseline characteristics to the treated patients.

Benefits

Famotidine may decrease the composite outcome of death or intubation (HR:0.42; 95%CI 0.21, 0.85; Very low CoE); however, the evidence is very uncertain.

Harms

Famotidine is well tolerated. Common adverse events include diarrhea or constipation but occur in less than 5% of people. Severe adverse events occur in less than 1% of persons taking famotidine.

Other considerations

The panel determined that the certainty of evidence to be very low due to concerns with risk of bias, imprecision, and possible publication bias. The panel agreed that critically ill patients (i.e., mechanically ventilated) may have been more likely to receive PPIs than famotidine, thus potentially allocating more prognostically favorable patients to the famotidine group; however, the study did not report a protective effect associated with the use of PPIs.

Conclusions and research needs for this recommendation

The guideline panel suggests against famotidine for the sole purpose of treating COVID-19, unless in the context of a clinical trial. Additional clinical trials are needed to inform research for treatment with famotidine for patients with COVID-19.

Referenzen:
101. Freedberg DE, Conigliaro J, Wang TC, et al. Famotidine use is associated with improved clinical outcomes in hospitalized COVID-19 patients: A propensity score matched retrospective cohort study. Gastroenterology 2020.

Narrative summaries of treatments undergoing evaluation

In addition to the clinical questions addressed above, the panel identified several treatments currently undergoing evaluation for which additional data are needed to rate recommendations. Narrative summaries for these treatments are provided below.

HIV antivirals

In vitro antiviral activity of darunavir against SARS-CoV-2 showed no activity at clinically relevant concentrations. Three randomized, open-label clinical trials are currently listed on evaluating darunavir/cobicistat as a potential therapeutic option for COVID-19. Janssen, the manufacturer of darunavir/cobcistat has reported that one of these trials [102] has concluded that arunavir/cobicistat plus conventional treatments was not effective in achieving viral clearance at day seven post randomization, compared to conventional treatments alone. Clinical outcomes of this trial including rate of critical illness and mortality 14 days after randomization, have not been reported to date.

Lopinavir-ritonavir combined with interferon beta or other antivirals

Lopinavir-ritonavir is a combination of protease inhibitors for the treatment of HIV infection. Lopinavir-ritonavir has been shown to have in-vitro antiviral activity against betacoronaviruses such as SARS-CoV, and MERS-CoV [103-106]. Since lopinavir-ritonavir is not specifically designed for treatment of coronavirus, lopinavir-ritonavir alone may not demonstrate a difference from placebo in reducing viral load when treatment was initiated at a median of 13 days after symptoms onset [105]. In an open label treatment trial, lopinavirritonavir with ribavirin reduced the mortality and requirement of intensive care support of hospitalized SARS-CoV-1 patients compared with historical control [105]. Many interferons, especially interferon beta have been shown to have modest in-vitro antiviral activity against SARS-CoV and MERS-CoV [103, 104]. Lopinavir-ritonavir or interferon beta-1b has been shown to reduce viral load of MERS-CoV and improve lung pathology in a nonhuman primate model of common marmoset [106]. Lopinavir/ritonavir and interferon-β1b alone or in combination are being evaluated in clinical trials.

COVID-19 convalescent plasma for prophylaxis

There is a long history of using CP as treatment for infectious diseases, including severe viral lower respiratory tract infections [107]. Individuals who have recovered from SARS-CoV-2 infection may generate neutralizing antibodies [108, 109] that could have application to prevention of infection in certain settings, such as individuals with underlying conditions predisposing to severe disease and those with high-risk exposure. Monoclonal antibodies against other respiratory viruses have been shown to be protective against hospitalization in specific high-risk populations [110, 111] and animal models have suggested utility in prophylaxis against SARS-CoV-1 coronavirus infection [112]. There are some risks associated with the use of CP like transfusion-related acute lung injury or a theoretical risk of antibody-dependent enhancement of infection (ADE). Antibody-dependent enhancement of infection can occur in several viral diseases and involves an enhancement of disease in the presence of certain antibodies [113]. A trial from patients recovered from SARS-CoV-2 infection for use as prophylaxis in adults with a high-risk exposure is expected to begin recruiting shortly [114].

Ribavirin

There are only in vitro data available on the activity of ribavirin on SARS-CoV-2 currently. The EC50 (half maximal effective concentrations) was significantly higher than for chloroquine and remdesivir, so it appears less potent in vitro compared to these agents [16]. There are limited clinical studies in SARS-CoV-1 and MERS-CoV infections. In a systematic review of ribavirin treatment in patients infected with SARS-CoV-1, 26 studies were classified as inconclusive, and four showed possible harm [115]. In a retrospective observational study in patients with MERS-CoV infection, the combination of ribavirin and interferon, compared to no antiviral treatment, was not associated with improvement in the 90-day mortality or more rapid MERS-CoV RNA clearance [116].

Oseltamivir

Oseltamivir is a neuraminidase inhibitor used for prophylaxis and treatment of influenza. Given its specificity for an enzyme not found on coronaviruses, it is unclear what the mechanism of action would be against COVID-19. However, this has been used in combinations of antiviral therapy in Wuhan [117] and continues to be explored as a therapeutic option as part of combination regimens. Two trials evaluating combination regimens are underway in Wuhan [118, 119] as well as a trial in Thailand proposing different combinations [120]. None of the trials or case reports have examined oseltamivir as monotherapy.

Intravenous immunoglobulin

Intravenous immunoglobulin (IVIg) has been used as an adjuvant to treat a variety of pathogens either as a pooled product or in a concentrated more pathogen focused (hyperimmune) form. As the community from which a given batch of IVIg is derived from includes increasing numbers of individuals who have recovered from SARS-CoV-2, the possibility of protective antibodies being present in the pooled product is increased. However, the potential utility of IVIg for the treatment of SARS-CoV-2 is unknown at this time. Its use has been reported in a few patients with COVID-19 [121], but studies are needed to determine if there may be a role for IVIg in the treatment of SARS-CoV-2.

Should NSAIDS be stopped in patients with COVID-19?

The role of Nonsteroidal anti-inflammatory drugs (NSAIDs) in the management of SARSCoV2 has been discussed widely. Recent anecdotal reports and subsequent warnings from health officials have suggested against the use of NSAIDs in the care of patients with COVID-19; however, neither FDA, European Medicines Agency, or the World Health Organization have identified evidence linking NSAIDS to COVID-related clinical deterioration. Human coronaviruses, including SARS CoV-2, use ACE2 to bind to human targets and gain entry into target cells [122]. It has been theorized that NSAIDs, due to upregulation in ACE2 in human target cells, may lead to a more severe course of COVID-19 in those taking NSAIDs. While no causal evidence of adverse outcomes with NSAIDs in the management of COVID-19 have been published, there are well known risks of non-steroidal anti-inflammatory agents including cardiovascular, gastrointestinal and renal adverse events [123, 124]. In the setting of bacterial pneumonia, NSAIDs may impair recruitment of polymorphonuclear cells, resulting in a delayed inflammatory response and resolution of infection, however a causal relationship has not been established [125, 126]. RCTs are needed to better understand the safety of NSAIDS in the management of patients with COVID-19. One RCT is currently underway to evaluate the role of naproxen in those critically ill with COVID-19 [127].

Should ACE inhibitors and ARBs for hypertension be stopped in patients with COVID-19?

Angiotensin converting enzyme 2 (ACE2) is the receptor for SARS CoV-2 on human cells. Because angiotensin-converting enzyme (ACE) inhibitors and angiotensin receptor blockers (ARBs) may increase ACE2 expression, the possibility has been raised that these drugs may increase the likelihood of acquiring SARS-CoV-2 or may exacerbate the course of COVID-19. To date, however, there are no clinical data to support this hypothetical concern. For this reason, the American Heart Association, the Heart Failure Society of America and the American College of Cardiology all recommend that ACE inhibitors or ARBs be continued in people who have an indication for these medications [128].

Referenzen:

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113. Casadevall A, Pirofski LA. The convalescent sera option for containing COVID-19. J Clin Invest 2020; 130(4): 1545-8.
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116. Arabi YM, Shalhoub S, Mandourah Y, et al. Ribavirin and Interferon Therapy for Critically Ill Patients With Middle East Respiratory Syndrome: A Multicenter Observational Study. Clin Infect Dis 2019.

117. Chen N, Zhou M, Dong X, et al. Epidemiological and clinical characteristics of 99 cases of 2019 novel coronavirus pneumonia in Wuhan, China: a descriptive study. Lancet 2020; 395(10223): 507-13.
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National COVID-19 Clinical Evidence Taskforce, 2020 [8].

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

Zielsetzung/Fragestellung

To provide specific, patient-focused recommendations for the clinical care of people with suspected or confirmed COVID-19, where care for this patient group differs from usual care provided to patients with similar clinical conditions (pneumonia, severe acute respiratory distress, etc.).

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: We aim to publish an updated version of the guidelines each week until the end of September 2020.

Recherche/Suchzeitraum:

- Keine Angabe, ständige Aktualisierung

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.

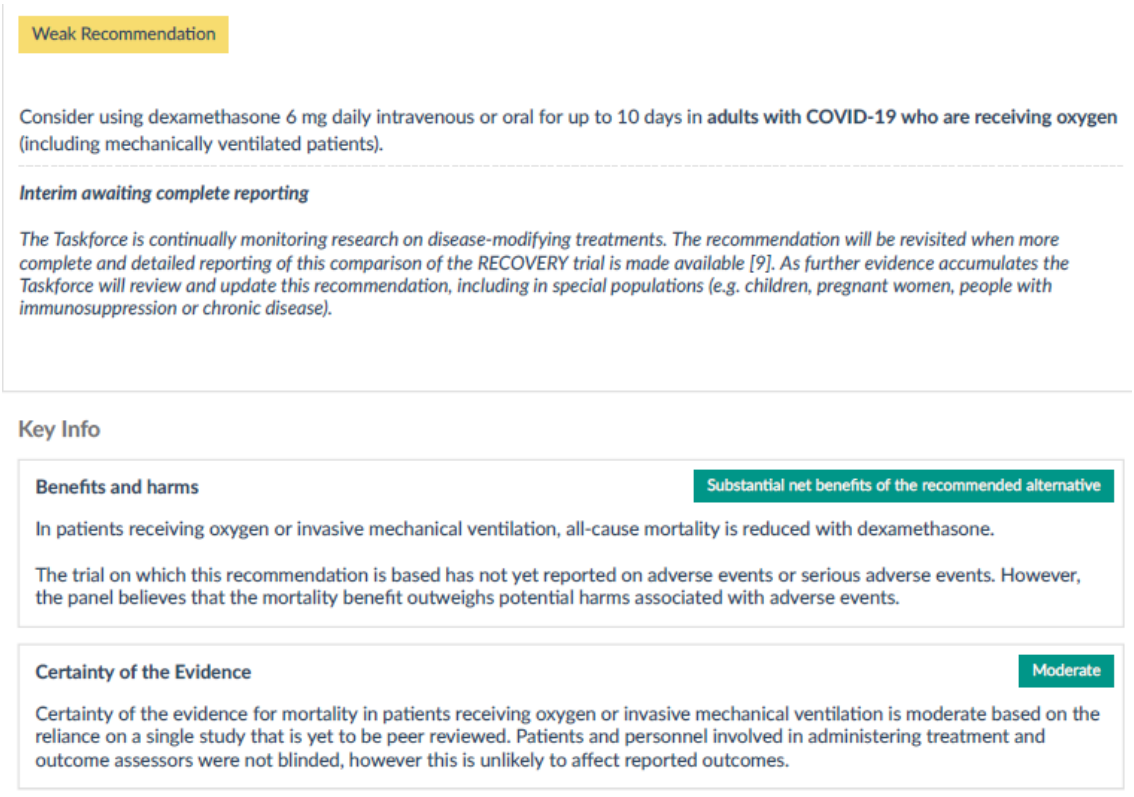
Sonstige methodische Hinweise

- We may, as the panels agree is appropriate, draw on studies providing indirect evidence from patients with SARS/MERS/pandemic influenza.

Recommendations

5 Disease-modifying treatments

5.1 Dexamethasone



Rationale

Due to a reduction in all-cause mortality, along with no important resource implications and the likely acceptability of the drug, we recommend that use of dexamethasone be considered for adults with COVID-19 who are receiving oxygen (including mechanically ventilated patients).

The conditional recommendation reflects that complete reporting of the results of the RECOVERY Trial are not yet available.[9]

Summary

Preliminary evidence indicates that dexamethasone probably decreases all-cause mortality in COVID-19 patients who require oxygen or invasive mechanical ventilation. In contrast, dexamethasone in patients who do not require oxygen may lead to increased mortality.

Evidence informing this recommendation comes from a single open-label randomised trial currently only available as preprint *[9]* that compared dexamethasone plus usual care to usual care alone in hospitalised patients with clinically suspected or laboratory-confirmed SARS-CoV-2 infection. Patients were originally restricted to adults 18 years of age or older, however this restriction was removed during recruitment. Six pregnant or breastfeeding women were included in the analyses, however it is unclear to which treatment arm they were assigned. Complete reporting of this trial is not yet available.

Outcomes reported include 28-day mortality, duration of hospital stay, number of patients discharged from hospital after 28 days, and the number of patients requiring mechanical ventilation. For mortality, subgroup analyses were conducted based on whether patients did not require oxygen, required oxygen, or required mechanical ventilation. The study has not yet reported on adverse events, serious adverse events or discontinuation of treatment due to adverse events.

Certainty of the evidence for all-cause mortality for patients not receiving oxygen is low. This judgement is based on serious imprecision due to the reliance on a single study and non-significant findings when the data were adjusted for age. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect this outcome.

Certainty of the evidence is moderate for all-cause mortality for patients receiving oxygen or receiving invasive mechanical ventilation. This judgement is based on reliance on a single study. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect reported outcomes.

Overall certainty of the evidence for other outcomes (mechanical ventilation requirement; discharge from hospital; duration of hospital stay) is moderate.

Weak Recommendation Against

Do not routinely use dexamethasone to treat **COVID-19 in adults who do not require oxygen.**

Interim awaiting complete reporting

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

The Taskforce is continually monitoring research on disease-modifying treatments. The recommendation will be revisited when more complete and detailed reporting of this comparison of the RECOVERY trial is made available [9]. As further evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms — Important harms

In patients who do not require oxygen, all-cause mortality may be higher with dexamethasone. The trial on which this recommendation is based has not yet reported on adverse events or serious adverse events.

Certainty of the Evidence — Low

Certainty of the evidence for mortality in patients who do not require oxygen is low based on very serious imprecision due to the reliance on a single study and the difference in the relative risk when using adjusted versus non-adjusted analysis. Patients, personnel involved in administering treatment and outcome assessors were not blinded, however this is unlikely to affect reported outcomes.

Rationale

Evidence suggests that the use of dexamethasone in patients with COVID-19 who do not require oxygen may increase the risk of all-cause mortality. We therefore recommend against the use of dexamethasone in this population, unless there is an alternative evidence-based indication for its use.

The conditional recommendation reflects that complete reporting of the results of the RECOVERY Trial are not yet available.[9]

Referenzen:

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Juszczak E, Baillie JK, Haynes R, Landray MJ : Effect of dexamethasone in hospitalized patients with COVID-19: preliminary report. medRxiv 2020/01/01; 2020.06.22.20137273

5.2 Baloxavir marboxil

Strong Recommendation Against

For people with COVID-19, only administer baloxavir marboxil in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms associated with the use of baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache.

Certainty of the Evidence Very Low

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

Rationale

There is currently limited evidence about the impact of baloxavir marboxil on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from a single randomised trial that compared baloxavir marboxil to standard care in patients with COVID-19 *[41]*. The study included 20 hospitalised adults concomitantly using lopinavir/ritonavir, darunavir/cobicistat and/or arbidol.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

The Therapeutic Goods Administration highlights several mild side effects associated with baloxavir marboxil, including diarrhoea, bronchitis, nausea, sinusitis and headache. In addition, post-marketing surveillance has identified cases of anaphylactic reactions, angioedema, vomiting and other gastrointestinal and skin/subcutaneous tissue disorders *[42]*.

Based on the available evidence, there remains significant uncertainty whether baloxavir marboxil is more effective and safer than standard care in treating patients with COVID-19.

Referenzen:
[41] Lou Y, Yao H, Hu Z : Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. medRxiv 2020

5.3 Favipiravir

Strong Recommendation Against

For people with COVID-19, only administer favipiravir in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

The safety profile for favipiravir is incompletely characterised in humans. As a result, there is uncertainty around the benefits and harms for patients with COVID-19.

Certainty of the Evidence Very Low

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

Rationale

There is currently limited evidence about the impact of favipiravir on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from a single randomised trial that compared favipiravir to standard care in patients with COVID-19 *[41]*. The study included 19 hospitalised adults concomitantly using lopinavir/ritonavir, darunavir/ cobicistat and/or arbidol.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and/or observed events and the reliance on a single study.

As of 6 May 2020, favipiravir (Avigan) is not approved for use in Australia. The safety profile for favipiravir is incompletely characterised in humans.

Based on the available evidence, there remains significant uncertainty whether favipiravir is more effective and safer than standard care in treating patients with COVID-19.

Referenzen:
[41] Lou Y, Yao H, Hu Z : Clinical outcomes and plasma concentrations of baloxavir marboxil and favipiravir in COVID-19 patients: an exploratory randomized, controlled trial. medRxiv 2020

5.4 Lopinavir/ritonavir

Strong Recommendation Against

For people with COVID-19, only administer lopinavir/ritonavir in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms — Important harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir/ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs.

Harms associated with short-term use have been reported in three trials *[26][27][12]*. These include transient elevation of alanine aminotransferase and gastrointestinal symptoms, such as diarrhoea.

Certainty of the Evidence — Very Low

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias and inconsistency, and very serious imprecision due to the low number of patients and/or the low number of observed events.

Rationale

There is currently limited evidence about the impact of liponavir/ritonavir on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations [5][7][10][11], we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from three randomised trials that compared lopinavir/ritonavir plus standard care to standard care alone in patients with COVID-19 *[26][27][12]*. One study included patients with severe illness *[27]*, another included patients with mild/moderate illness *[26]* and the third included patients with moderate or severe illness *[12]*.

Two studies provided data specific to mortality, respiratory failure or ARDS and requirement of mechanical ventilation or ECMO *[26][27]*. All studies provided data on adverse events and serious adverse events. Only one study reported data relating to clinical improvement at day 14 after treatment initiation *[27]*.

Certainty of the evidence for each outcome is very low. This judgement is based on: serious risk of bias due to lack of personnel blinding and selective outcome reporting; serious imprecision due to the low number of patients and/or low number of observed events; and serious inconsistency in respiratory failure/ARDS, adverse events and serious adverse events, which may be related to the difference in illness severity between the studies.

According to the Therapeutic Goods Administration there are well-known side effects and harms associated with lopinavir/ritonavir. Although most of the information on side effects and harms is derived from long-term use, potential acute harms include: gastrointestinal symptoms, hyperglycaemia, pancreatitis, lipid elevations, hepatic impairment, QT interval prolongation, and PR interval prolongation. Chronic harms include: increased risk of bleeding in patients with haemophilia, fat redistribution and immune reconstitution syndrome, among others. Lopinavir/ritonavir interacts with CYP3A and may result in increased plasma concentrations of the other drugs *[10]*.

Based on the available evidence, there remains significant uncertainty whether lopinavir/ritonavir is more effective and safer than standard care in treating patients with COVID-19.

Referenzen:
[5] Australian and New Zealand Intensive Care Society (ANZICS) : COVID-19 Guidelines (version 1). 2020; Website
[7] Australasian Society for Infectious Diseases (ASID) : Interim guidelines for the clinical management of COVID-19 in adults (version 1). 2020; Website

[10] Therapeutic Goods Administration : Australian Product Information: Kaletra (lopinavir/ritonavir) tablets and oral solution (version 32). 2019;Website
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[26] Li Y, Xie Z, Lin W, Cai W, Wen C, Guan Y, Mo X, Wang J, Wang Y, Peng P, Chen X, Hong W, Xiao G, Liu J, Zhang L, Hu F, Li F, Zhang F, Deng X, Li L : Efficacy and safety of lopinavir/ritonavir or arbidol in adult patients with mild/moderate COVID-19: an exploratory randomized controlled trial. Med 2020; 2020.03.19.20038984Website
[27] Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, Ruan L, Song B, Cai Y, Wei M, Li X, Xia J, Chen N, Xiang J, Yu T, Bai T, Xie X, Zhang LI, Li C, Yuan YE, Chen H, Li H, Huang H, Tu S, Gong F, Liu Y, Wei Y, Dong C, Zhou F, Gu X, Xu J, Liu Z, Zhang YI, Li H, Shang L, Wang KE, Li K, Zhou X, Dong X, Qu Z, Lu S, Hu X, Ruan S, Luo S, Wu J, Peng LU, Cheng F, Pan L, Zou J, Jia C, Wang J, Liu X, Wang S, Wu X, Ge Q, He J, Zhan H, Qiu F, Guo LI, Huang C, Jaki T, Hayden FG, Horby PW, Zhang D, Wang C : A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. New England Journal of Medicine 2020

5.5 Remdesivir

5.5.1 Remdesivir for adults

Weak Recommendation

Whenever possible remdesivir should be administered in the context of a randomised trial with appropriate ethical approval. Use of remdesivir for adults with moderate, severe or critical COVID-19 outside of a trial setting may be considered.

For information on dosages, length of treatment and characteristics of the patients in the trials used for this recommendation, see the Practical info tab below.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation

Benefits and harms — Small net benefit, or little difference between alternatives

The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. However, there remains uncertainty around the benefits and harms of remdesivir for patients with COVID-19. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Certainty of the Evidence — Low

Certainty of the evidence for most reported outcomes is low or very low due to serious risk of bias and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of moderate certainty.

Rationale

The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery. Because of this the Taskforce gives a conditional recommendation for the use of remdesivir both within and outside the context of a randomised trial.

The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines *[16][19][38]*. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. The Taskforce recommendation to consider use of remdesivir outside of a randomised trial therefore applies to adult patients with moderate, severe or critical COVID-19.

Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

Clinical Question/ PICO

Population:	People with COVID-19
Intervention:	Remdesivir
Comparator:	Placebo

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in patients with COVID-19 *[16][38]*. One study included 1063 patients with moderate to critical illness *[16]* and the other included 236 patients with severe to critical illness *[38]*. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required.

Certainty of the evidence for most outcomes is low (all-cause mortality at day 14 and 28, respiratory failure or ARDS, time to recovery and adverse events) or very low (septic shock, clinical recovery and adverse events leading to discontinuation). The exception is serious adverse events, which is of moderate certainty. These judgements are based on lack of personnel blinding *[16]* (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies.

It is important to note that Beigel 2020 *[16]* provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating patients with COVID-19.

Clinical Question/ PICO

Population:	Patients with severe COVID-19
Intervention:	Remdesivir 5-day treatment
Comparator:	Remdesivir 10-day treatment

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for each outcome is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interacive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*.

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

Referenzen

[16] Beigel JH, Tomashek KM, Dodd LE : Remdesivir for the treatment of Covid-19: preliminary report. New England Journal of Medicine 2020

[19] Goldman JD, Lye DC, Hui DS, Marks KM, Bruno R, Montejano R, Spinner CD, Galli M, Ahn M-Y, Nahass RG, Chen Y-S, SenGupta D, Hyland RH, Osinusi AO, Cao H, Blair C, Wei X, Gaggar A, Brainard DM, Towner WJ, Muñoz J, Mullane KM, Marty FM, Tashima KT, Diaz G, Subramanian A : Remdesivir for 5 or 10 days in patients with severe Covid-19. New England Journal of Medicine 2020;

[38] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu YI, Luo G, Wang KE, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang YI, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang YI, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;

5.5.2 Remdesivir for pregnant patients

Weak Recommendation Against

Use of remdesivir for pregnant patients with COVID-19 outside of a trial setting should not be considered routinely.

As pregnant patients are often excluded from clinical trials, use of remdesivir in this population would be outside a clinical trial setting. Pregnant patients receiving remdesivir should nonetheless be enrolled in national COVID-19 registries. Currently, there is no direct evidence of the effects of remdesivir in pregnant and breastfeeding patients. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

Benefits and harms — Small net benefit, or little difference between alternatives

There remains uncertainty around the benefits and harms of remdesivir for pregnant patients with COVID-19. Evidence from a trial comparing a 10-day to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point.

Certainty of the Evidence — Very Low

Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

Rationale

There is currently no direct evidence about the impact of remdesivir on outcomes relevant to pregnant and breastfeeding patients with COVID-19 and insufficient data on safety. The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery in non-pregnant adults.

The severity of disease is an important factor when considering the use of remdesivir. For pregnant patients with severe or critical COVID-19, the harm to benefit ratio may differ compared to pregnant patients with mild or moderate illness. The populations in the three studies published to date approximate to the moderate, severe and critical illness categories outlined in these guidelines *[16][19][38]*. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that their results could inform the length of treatment at this point.

Clinical Question/ PICO

Population:	Pregnant patients with COVID-19 [adapted from general adult population]
Intervention:	Remdesivir
Comparator:	Placebo

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included pregnant or breastfeeding patients. One study included 1063 patients with moderate to critical illness *[16]* and the other included 236 patients with severe to critical illness *[38]*. The evidence is judged to be applicable to pregnant and breastfeeding patients.

In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. Patients were 18 years of age or older and both studies excluded pregnant and breastfeeding patients. The

mean age of patients receiving remdesivir ranged from 58 to 66 years, with the proportion of women ranging from 35% to 44%. The mean age of those receiving standard care ranged from 59 to 64 years, with the proportion of women ranging from 35% to 36%.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding *[16]* (which is considered of no relevance in mortality), serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies, and indirectness (due to the absence of pregnant or breastfeeding patients in included studies).

It is important to note that Beigel 2020 *[16]* provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in pregnant and breastfeeding patients.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating pregnant patients with COVID-19.

Clinical Question/ PICO

Population:	Pregnant patients with severe COVID-19 [adapted from general adult population]
Intervention:	Remdesivir 5-day treatment
Comparator:	Remdesivir 10-day treatment

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19; the trial did not include pregnant patients. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The evidence is judged to be applicable to pregnant patients.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interacive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), very serious imprecision (only one study with few patients and/or few events) and serious indirectness (population included adults who were not pregnant).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*.

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

Referenzen

[14] European Medicines Agency: Remdesivir Gilead: summary on compassionate use EMEA/H/K/5622/CU. 2020
[16] Beigel JH, Tomashek KM, Dodd LE: Remdesivir for the treatment of Covid-19: preliminary report. New England Journal of Medicine 2020
[38] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu YI, Luo G, Wang KE, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang YI, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang YI, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;

5.5.3 Remdesivir for children or adolescents

Weak Recommendation Against

Use of remdesivir for children or adolescents with COVID-19 outside of a trial setting should not be considered routinely.

If treatment is considered—in exceptional circumstances—it should be in consultation with a clinical reference group, such as the ANZPID COVID-19 Clinical Reference Group. Informed consent from parents/caregivers should also be obtained. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Information about the patients and the intervention (dosages, duration) in the trials used for this recommendation can be found in the Practical info tab.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation.

Benefits and harms — Small net benefit, or little difference between alternatives

The two trials of remdesivir versus standard care provide preliminary evidence suggesting that remdesivir as a 10-day treatment has an acceptable safety profile. A third trial that compared a 10-day course to a 5-day course was too uncertain to inform decisions regarding length of treatment at this point. The results are based on adults (aged 44 to 75 years)—the trials did not include children and adolescents. There remains uncertainty around the benefits and harms of remdesivir for children and adolescents with COVID-19.

Certainty of the Evidence — Very Low

Certainty of the evidence for most reported outcomes is very low due to serious risk of bias, indirectness and either serious imprecision or inconsistency in the direction of effect between studies. The exception is serious adverse events, which is considered to be of low certainty.

Rationale

The effect of remdesivir on mortality is uncertain but it may decrease the time to recovery and the risk of serious adverse events in adults. Currently, there is no direct evidence for the use of remdesivir in children or adolescents. Because of this the Taskforce gives a conditional recommendation against the use of remdesivir outside the context of a randomised trial for children and adolescents.

The populations in the three studies published to date (adults aged 44-75 years) approximate to the moderate, severe and critical illness categories outlined in this guideline. The studies had insufficient power to perform adequate subgroup analyses. Beigel 2020, however, reported small numerical differences between study arms in the outcomes of patients with critical COVID-19, but no statistically significant difference in the primary outcome (time to recovery) by baseline disease severity. Goldman 2020 compared a 5-day to a 10-day course of treatment, but since there is no established benefit for either approach yet, it remains uncertain that these results can inform the length of treatment.

Clinical Question/ PICO

Population: Children and adolescents with COVID-19 [adapted from general adult population]

Intervention: Remdesivir
Comparator: Placebo

Summary

Evidence informing this recommendation comes from two randomised trials that compared remdesivir to placebo in adult patients with COVID-19; neither trial included children or adolescents. One study included 1063 patients with moderate to critical illness [14] and the other included 236 patients with severe to critical illness [31]. In both studies, randomisation was stratified by the level of disease severity, and in particular whether respiratory support was required. In both studies, patients had to be 18 years of age or older to be included (mean age ranged from 59 to 66 years in the remdesivir group and 59 to 64 years in the control group). The evidence is judged to be applicable to children and adolescents.

Certainty of the evidence for the majority of outcomes is very low. The exception is serious adverse events, which is considered to be of low certainty. These judgements are based on lack of personnel blinding (which is considered of no relevance in mortality) and either serious imprecision (due to low number of patients and/or observed events, reliance on a single study or wide confidence intervals) or inconsistency in the direction of effect between studies. All outcomes were downgraded for indirectness as results were based on adults.

It is important to note that Beigel 2020 *[16]* provides preliminary results only and does not provide data for 28-day mortality. As such, this study will remain under surveillance and additional results will be included when they become available.

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*. There is currently insufficient evidence to assess adverse outcomes following treatment with remdesivir in children or adolescents.

Based on the available evidence, it remains uncertain as to whether remdesivir is more effective and safer than placebo in treating children or adolescents with COVID-19.

Clinical Question/ PICO

Population: Children and adolescents with severe COVID-19 [adapted from general adult population]
Intervention: Remdesivir 5-day treatment
Comparator: Remdesivir 10-day treatment

Summary

Evidence informing this recommendation comes from a single randomised trial that compared 5-day to 10-day treatment with remdesivir in hospitalised patients with severe COVID-19; the trial did not include children or adolescents. Patients were eligible if they were at least 12 years of age with PCR-confirmed SARS-CoV-2 infection before randomisation, had radiographic evidence of pulmonary infiltrates and oxygen saturation of 94% or less while breathing ambient air or were receiving supplemental oxygen. The median age reported in the trial was 61 years [IQR 50-69] for the 5-day group and 62 years [IQR 50-71] for the 10-day group. The evidence is judged to be applicable to children and adolescents.

The primary outcome was clinical status on day 14 using a 7-point scale (ranging from hospital discharge to death). Secondary outcomes included adverse events, serious adverse events (including acute respiratory failure/ARDS and septic shock), discontinuation of treatment due to adverse events and clinical recovery.

Certainty of the evidence for all reported outcomes is very low. This judgement is based on serious risk of bias (eligible patients were randomised using an interacive web response system; however no further details were provided and patients in the 10-day group had significantly worse clinical status than those in the 5-day group at enrolment; patients, personnel administering the intervention and outcome assessors were not blinded), and very serious imprecision (only one study with few patients and/or few events).

It is important to note that this publication only presents initial results from the first 400 patients in a trial that includes 6000 patients (NCT04292899). This analysis will be updated when results from the full cohort are available (the primary completion date of the trial is listed as June 2020).

The safety profile for remdesivir is incompletely characterised in humans. Preliminary results from manufacturer-led trials indicate that patients may experience side effects, including transient elevations in alanine aminotransferase and aspartate transaminase, headache, nausea, phlebitis, constipation, ecchymosis, pain in extremity and possible hypotension *[14]*.

Based on the available evidence, it remains uncertain whether a 5-day treatment schedule of remdesivir is more effective and safer than a 10-day treatment schedule.

Referenzen

[14] European Medicines Agency: Remdesivir Gilead: summary on compassionate use EMEA/H/K/5622/CU. 2020
[16] Beigel JH, Tomashek KM, Dodd LE: Remdesivir for the treatment of Covid-19: preliminary report. New England Journal of Medicine 2020
[38] Wang Y, Zhang D, Du G, Du R, Zhao J, Jin Y, Fu S, Gao L, Cheng Z, Lu Q, Hu YI, Luo G, Wang KE, Lu Y, Li H, Wang S, Ruan S, Yang C, Mei C, Wang YI, Ding D, Wu F, Tang X, Ye X, Ye Y, Liu B, Yang J, Yin W, Wang A, Fan G, Zhou F, Liu Z, Gu X, Xu J, Shang L, Zhang YI, Cao L, Guo T, Wan Y, Qin H, Jiang Y, Jaki T, Hayden FG, Horby PW, Cao B, Wang C : Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. Lancet 2020;

5.6 Ruxolitinib

Strong Recommendation Against

For people with COVID-19, only administer ruxolitinib in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms Important harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms. Although most of the information on side effects and harms is derived from long-term use, potential harms include thrombocytopaenia and other haematological adverse reactions and increased incidence of bacterial and other infections.

Certainty of the Evidence Very Low

Certainty of the evidence is low for mortality and very low for all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).

Rationale

There is currently limited evidence about the impact of ruxolitinib on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that thistreatments should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from a single randomised trial that compared ruxolitinib to placebo (vitamin C) in 41 hospitalised adult patients with severe COVID-19 *[48]*.

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding of outcome assessors, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of ruxolitinib, including thrombocytopaenia and other haematological adverse reactions and increased incidence of bacterial and other infections. Cases of progressive multifocal leukoencephalopathy (PML) and non-melanoma skin cancer have also been reported in patients treated with ruxolitinib *[51]*.

Based on the available evidence, there remains significant uncertainty whether ruxolitinib is more effective and safer than standard care in treating patients with COVID-19.

Referenzen

[48] Cao Y, Wei J, Zou L: Ruxolitinib in treatment of severe coronavirus disease 2019 (COVID-2019): a multicenter, single-blind, randomized controlled trial. Journal of Allergy and Clinical Immunology 2020; Pubmed JournalWebsite

[51] Therapeutic Goods Administration : Australian Product Information: Jakavi (ruxolitinib).

5.7 Hydroxychloroquine

Strong Recommendation Against

For people with COVID-19, only administer hydroxychloroquine in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Several cohort studies exploring harms have been published and we are currently assessing the evidence. One study has subsequently been retracted [32] and is not being considered by the Taskforce.

Key Info

Benefits and harms — **Important harms**

In addition to uncertainty around the benefits for patients 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. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms.

Certainty of the Evidence — **Very Low**

Certainty of the evidence for each outcome is very low due to serious risk of bias and the low numbers of trials and patients for some outcomes. There was also inconsistency in the results across trials.

Rationale

There is currently limited evidence about the impact of hydroxychloroquine on patient-relevant outcomes for COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations [5][7][10][11], we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from three randomised trials that compared hydroxychloroquine sulfate plus standard care to standard care alone *[24][25][28]*. Two studies focused on patients experiencing moderate illness *[24][25]* and one on patients with mild, moderate and severe illness *[28]*.

Each study was limited in the number of relevant outcomes reported. All three reported the number of individuals experiencing one or more adverse events (two studies reported the incidence of severe adverse events [13]*[28]* and virological clearance at day 7 after treatment initiation [12]*[28]*, one study reported mortality *[25]*). None reported the incidence of respiratory failure/ARDS or requirement for mechanical ventilation/ECMO.

Certainty of the evidence for each outcome is very low. This judgement is based on: serious risk of bias due to unclear reporting of sequence generation and allocation concealment *[24][25]* and lack of blinding of patients and personnel *[28]*; and very serious imprecision due to the low number of patients and/or low number of observed events. The exception was adverse events, in which certainty was low due to serious risk of bias and imprecision.

According to the Therapeutic Goods Administration known acute harms for hydroxychloroquine include prolonged QT interval and lowered convulsive threshold. Long-term harms of relevance include retinopathy and chronic cardiac myopathy *[30]*. There are several known and potential interactions with other drugs *[30]*. Overdose of hydroxychloroquine may have potentially fatal complications. In pregnancy, it is only recommended when benefits outweigh harms *[30]*.

Based on the available evidence, there remains significant uncertainty whether hydroxychloroquine/chloroquine is more effective and safer than standard care in treating patients with COVID-19.

Referenzen

[5] Australian and New Zealand Intensive Care Society (ANZICS) : COVID-19 Guidelines (version 1). 2020;Website
[7] Australasian Society for Infectious Diseases (ASID) : Interim guidelines for the clinical management of COVID-19 in adults (version1). 2020; Website
[10] Therapeutic Goods Administration : Australian Product Information: Kaletra (lopinavir/ritonavir) tablets and oral solution (version 32). 2019;Website
[11] Lopinavir/Ritonavir for COVID-19.
[12] Zheng F, Zhou Y, Zhou Z, Ye F, Huang B, Huang Y, Ma J, Zuo QI, Tan X, Xie J, Niu P, Wang W, Xu Y, Peng F, Zhou N, Cai C, Tang W, Xiao X, Li YI, Zhou Z, Zhou Z, Jiang Y, Xie Y, Tan W, Gong G : A novel protein drug, Novaferon, as the potential antiviral drug for COVID-19. medRxiv 2020; 2020.04.24.20077735
[13] Remdesivir for COVID-19
[24] Chen J, Liu D, Lui L : A pilot study of hydroxychloroquine in treatment of patients with moderate COVID-19. Zhejiang Da Xue Xue Bao Yi Xue Ban 2020;49(2):215-9 Pubmed Journal
[25] Chen Z, Hu J, Zhang Z, Jiang S, Han S, Yan D, Zhuang R, Hu B, Zhang Z : Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. medRxiv 2020; 2020.03.22.20040758
[28] Tang W, Cao Z, Han M, Wang Z, Chen J, Sun W, Wu Y, Xiao W, Liu S, Chen E, Chen W, Wang X, Yang J, Lin J, Zhao Q, Yan Y, Xie Z, Li D, Yang Y, Liu L, Qu J, Ning G, Shi G, Xie Q : Hydroxychloroquine in patients with mainly mild to moderate coronavirus disease 2019: open label, randomised controlled trial. BMJ 2020;
[30] Therapeutic Goods Administration : Australian Product Information: Plaquenil (hydroxychloroquine sulfate). Dec 2019

5.8 Convalescent plasma

Strong Recommendation Against

For people with COVID-19, only administer convalescent plasma in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

There is uncertainty around the benefits and harms associated with the use of convalescent plasma for patients with COVID-19.

Certainty of the Evidence Very Low

Certainty of the evidence is low for mortality and very low all other outcomes due to serious risk of bias (lack of blinding of outcome assessors) and very serious imprecision (due to the low number of patients and observed events).

Rationale

There is currently limited evidence about the impact of convalescent plasma on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that this treatment should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from a single randomised trial that compared convalescent plasma to standard care in 103 hospitalised adult patients with severe or critical COVID-19 *[46]*.

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes This judgement is based on serious risk of bias due to lack of blinding, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

Information pertaining to the safety of convalescent plasma for the treatment of COVID-19 is not currently available. The present study did not clearly state the total number of adverse events associated with its use.

Based on the available evidence, there remains significant uncertainty whether convalescent plasma is more effective and safer than standard care in treating patients with COVID-19.

Referenzen:
[46] Li L, Zhang W, Hu YU, Tong X, Zheng S, Yang J, Kong Y, Ren L, Wei Q, Mei H, Hu C, Tao C, Yang RU, Wang J, Yu Y, Guo Y, Wu X, Xu Z, Zeng LI, Xiong N, Chen L, Wang J, Man N, Liu YU, Xu H, Deng E, Zhang X, Li C, Wang C, Su S, Zhang L, Wang J, Wu Y, Liu Z: Effect of convalescent plasma therapy on time to clinical improvement in patients with severe and life-threatening COVID-19: a randomized clinical trial. JAMA 2020;

5.9 Interferon β-1a

Strong Recommendation Against

For people with COVID-19, only administer interferon β-1a in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms — Important harms

In addition to uncertainty around the benefits for patients with COVID-19, there are well-known side effects and harms associated with the use of interferon β-1a including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation.

Certainty of the Evidence — Very Low

Certainty of the evidence is low for mortality and very low for all other outcomes due to very serious risk of bias (lack of blinding, non-reporting of allocation method and potential for missing outcome data) and very serious imprecision (low number of patients and observed events).

Rationale

There is currently limited evidence about the impact of interferon β-1a on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

We therefore recommend that thistreatments should only be administered in the context of randomised trials with appropriate ethical approval.

Summary

Evidence informing this recommendation comes from a single randomised trial that compared interferon beta-1a with standard care in 81 hospitalised adult patients with severe COVID-19 *[47]*.

Certainty of the evidence is low for all-cause mortality and very low for all other outcomes. This judgement is based on serious risk of bias due to lack of blinding and insufficient information regarding allocation concealment and potential missing outcome data, and very serious imprecision due to the low number of patients and observed events and the reliance on a single study. Mortality was not downgraded for risk of bias as this outcome is unlikely to be biased by lack of blinding.

The Therapeutic Goods Administration highlights several potential side effects associated with the use of interferon beta-1a, including thrombotic microangiopathy, hepatic injury, nephrotic syndrome and depression with suicidal ideation. The use of interferon beta-1a is also associated with immune reactions that can produce flu-like symptoms *[49][50]*.

Based on the available evidence, there remains significant uncertainty whether interferon beta-1a is more effective and safer than standard care in treating patients with COVID-19.

Referenzen:
[47] Davoudi-Monfared E, Rahmani H, Khalili H : Efficacy and safety of interferon beta -1a in treatment of severe COVID-19: a randomized clinical trial. MedRxiv 2020; Website
[49] Therapeutic Goods Administration: Australian Product Information: Rebif (interferon beta-1a). 2020; Website
[50] Therapeutic Goods Administration: Australian Product Information: Avonex (interferon beta-1a). 2019;

5.10 Other disease-modifying treatments

Consensus Recommendation

For people with COVID-19, only administer disease-modifying treatments in the context of randomised trials with appropriate ethical approval.

The Taskforce is continually monitoring research on disease-modifying treatments. As evidence accumulates regarding the use of these treatments, the Taskforce will review and update this recommendation, including in special populations (e.g. children, pregnant women, people with immunosuppression or chronic disease).

Key Info

Benefits and harms

Currently, there is no direct evidence available to inform the potential benefits or harms of other disease-modifying treatments in patients with COVID-19.

Certainty of the Evidence

We have no COVID-19 specific randomised trials for many of the potential disease-modifying treatments.

Rationale

There is currently limited evidence about the impact of other disease-modifying treatments on patient-relevant outcomes in COVID-19.

The guideline panel has significant concerns about the potential harms of unproven treatments, including the possibility of adverse effects.

In line with the ANZICS, ASID, AHPPC and IDSA recommendations*[5][7][22][23]*, we therefore recommend that disease-modifying treatments should only be administered in the context of randomised trials with appropriate ethical approval.

Adaptation

The recommendation for use of antivirals and other disease-modifying treatments is adapted from published recommendations by ANZICS [5], Surviving Sepsis Campaign *[54]*, JAMA [25], Institute of Tropical Medicine (Belgium) [26], Department of Infectious Diseases at Austin Health (Australia), BMJ Best Practice [6], Alfred Health (Australia) [4], Australasian Society of Infectious Diseases [7], National Institute for the Infectious Diseases (Italy) [3] and Zhejiang University School of Medicine (China) [2]

Referenzen

[2] First Affiliated Hospital, Zhejiang University School of Medicine: Handbook of COVID-19 Prevention and Treatment. 2020;
[3] Nicastri E, Petrosillo N, Bartoli TA, Lepore L, Mondi A, Palmieri F, D'Offizi G, Marchioni L, Murachelli S, Ippolito G, Antinori A: National Institute for the Infectious Diseases "L. Spallanzani" IRCCS. Recommendations for COVID-19 Clinical Management. Infectious Disease Reports 2020;12(1): Pubmed Journal
[4] Alfred Health: Clinical management guideline for hospitalised patients on the ward with COVID-19 (version 5). 2020;
[5] Australian and New Zealand Intensive Care Society (ANZICS): COVID-19 Guidelines (version 1). 2020; Website
[6] Beeching NJ, Fletcher TE, Fowler R: BMJ Best Practice: COVID-19. BMJ 2020; [5] Australian and New Zealand Intensive Care Society (ANZICS): COVID-19 Guidelines (version 1). 2020; Website
[7] Australasian Society for Infectious Diseases (ASID): Interim guidelines for the clinical management of COVID-19 in adults (version1). 2020; Website
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7. Respiratory support

Consensus Recommendation

Guiding principles of care
For patients with COVID-19 for whom respiratory support (HFNO/NIV) is being considered, decisions should balance likelihood of patient benefit against the risk of infection for healthcare workers. For patients with COVID-19 receiving respiratory support (HFNO/NIV) or requiring intubation, use single rooms or negative pressure rooms wherever possible and ensure contact, droplet and airborne precautions are in place.

The relative risk of infection to healthcare workers associated with specific oxygen therapies remains uncertain and may vary from site to site.

7.1 High-flow nasal oxygen therapy

Recommendation Strength Not Set

High-flow nasal oxygen (HFNO) therapy is a form of respiratory support where oxygen is delivered, often in conjunction with compressed air and humidification. It delivers high flow oxygen via large diameter nasal cannula that is humidified and heated. Flow rates can be given up to 60 L/min in adults and 25 L/min in children with an oxygen/air blender supplying oxygen at 21-100%.

High-flow humidified oxygen should be considered when unable to maintain SaO2 ≥ 92% despite conventional oxygen delivery at > 6 L/min or an FiO2 0.4

Strong Recommendation

In **negative pressure rooms**, use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

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

Weak Recommendation

In **single rooms** or **shared ward spaces with cohorting of confimed COVID-19 patients only**, consider using high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

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

Strong Recommendation Against

In **shared wards** or **emergency department cubicles** do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

Strong Recommendation Against

During **inter-hospital patient transfer/retrieval** do not use high-flow nasal oxygen (HFNO) therapy for patients with hypoxaemia associated with COVID-19.

7.2 Non-invasive ventilation

Recommendation Strength Not Set

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

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

Consensus Recommendation

In **negative pressure rooms**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Consensus Recommendation

In **single rooms** or **shared ward spaces with cohorting of confirmed COVID-19 patients only**, consider using NIV therapy for patients with hypoxaemia associated with COVID-19, ensuring it is used with caution and strict attention is paid to staff safety.

Consensus Recommendation

In **shared wards or emergency department cubicles**, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

Consensus Recommendation

During inter-hospital patient transfer/retrieval, do not use NIV therapy for patients with hypoxaemia associated with COVID-19.

Consensus Recommendation

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

7.3 Respiratory management of the deteriorating patient

Consensus Recommendation

In patients with COVID-19 who are deteriorating, consider early endotracheal intubation and invasive mechanical ventilation.

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

7.4 Videolaryngoscopy

Weak Recommendation

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

7.5 Neuromuscular blockers

Recommendation Strength Not Set

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

Weak Recommendation Against

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

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

7.6 Positive end-expiratory pressure

Consensus Recommendation

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

7.7 Prone positioning

Recommendation Strength Not Set

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

Consensus Recommendation

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimising ventilation, consider prone positioning.

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

Consensus Recommendation

For adults with COVID-19 and respiratory symptoms who are receiving any form of supplemental oxygen therapy and have not yet been intubated, consider prone positioning. When positioning a patient in prone, ensure it is used with caution and close monitoring of the patient. Patients who are deteriorating should be considered for early endotracheal intubation and invasive mechanical ventilation.

7.8 Recruitment manoeuvres

Recommendation Strength Not Set

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

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

Consensus Recommendation

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

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

7.9 Extracorporeal membrane oxygenation

Recommendation Strength Not Set

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

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

Consensus Recommendation

In mechanically ventilated adults with COVID-19 and refractory hypoxaemia (despite optimising ventilation, use of rescue therapies and proning), consider using venovenous extracorporeal membrane oxygenation (VV ECMO) if available, or referring the patient to an ECMO centre.

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

4 Detaillierte Darstellung der Recherchestrategie

Cochrane Library - Cochrane Database of Systematic Reviews (Issue 6 of 12, June 2020) am 29.06.2020

#	Suchfrage
#1	MeSH descriptor: [Coronavirus Infections] explode all trees
#2	MeSH descriptor: [Pneumonia, Viral] explode all trees
#3	MeSH descriptor: [Severe Acute Respiratory Syndrome] explode all trees
#4	MeSH descriptor: [Coronavirus] explode all trees
#5	MeSH descriptor: [SARS Virus] explode all trees
#6	(coronavirus* OR (corona NEXT virus*)):ti,ab,kw
#7	(Covid19 OR "Covid 19" OR 2019ncov OR 19ncov OR cov2 OR ncov19 OR ncov2019 OR (ncov NEAR/3 2019) OR (ncov NEAR/3 19)):ti,ab,kw
#8	((cov*) NEAR/3 (novel OR new OR 2019 OR 19 OR infection* OR disease* OR wuhan OR pneumonia* OR pneumonitis OR SARS OR SARS2)):ti,ab,kw
#9	(viral OR virus*):ti,ab,kw AND (pneumonia* OR pneumonitis OR ((Lung* OR pulmonary) AND inflammation*)):ti,ab,kw
#10	("Severe Acute Respiratory Syndrome" OR SARS OR "severe acute respiratory infection" OR "severe acute respiratory infections" OR SARI):ti,ab,kw
#11	{OR #1-#10}
#12	#11 with Cochrane Library publication date Between Jun 2015 and Jun 2020

Systematic Reviews in Medline (PubMed) am 29.06.2020

#	Suchfrage
1	COVID-19 drug treatment[Supplementary Concept]
2	Coronavirus Infections/therapy[mh:noexp] OR Coronavirus Infections/drug therapy[mh:noexp] OR Coronavirus Infections/rehabilitation[mh:noexp] OR Coronavirus Infections/complications[mh:noexp]
3	"Pneumonia, Viral"/therapy[MeSH Terms]
4	Severe Acute Respiratory Syndrome/therapy[MeSH Terms]
5	"COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]
6	Coronavirus[MeSH Terms] OR SARS Virus[MeSH Terms]
7	Coronavirus[tiab] OR corona virus*[tiab]
8	Covid19[tiab] OR "Covid 19"[tiab] OR 2019ncov[tiab] OR 19ncov[tiab] OR cov2[tiab] OR ncov19[tiab] OR ncov2019[tiab] OR (ncov[tiab] AND 2019[tiab]) OR (ncov[tiab] AND 19[tiab])
9	(cov[tiab]) AND (novel[tiab] OR new[tiab] OR 2019[tiab] OR 19[tiab] OR infection*[tiab] OR disease*[tiab] OR wuhan[tiab] OR pneumonia*[tiab] OR pneumonitis[tiab] OR SARS[tiab] OR SARS2[tiab])
10	(Viral[tiab] OR virus*[tiab]) AND (pneumonia*[tiab] OR pneumonitis[tiab] OR ((Lung*[tiab] OR pulmonary[tiab]) AND inflammation*[tiab]))

11	"Severe Acute Respiratory Syndrome"[tiab] OR SARS[tiab] OR "severe acute respiratory infection"[tiab] OR "severe acute respiratory infections"[tiab] OR SARI[tiab]
12	#5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11
13	(#12) AND ((treatment*[tiab] OR treating[tiab] OR treated[tiab] OR treat[tiab] OR treats[tiab] OR treatab*[tiab] OR therapy[tiab] OR therapies[tiab] OR therapeutic*[tiab] OR monotherap*[tiab] OR polytherap*[tiab] OR pharmacotherap*[tiab] OR effect*[tiab] OR efficacy[tiab] OR management[tiab] OR drug*[tiab]))
14	#1 OR #2 OR #3 OR #4 OR #13
15	(#14) AND (((Meta-Analysis[ptyp] OR systematic[sb] OR ((systematic review [ti] OR meta-analysis[pt] OR meta-analysis[ti] OR systematic literature review[ti] OR this systematic review[tw] OR pooling project[tw] OR (systematic review[tiab] AND review[pt]) OR meta synthesis[ti] OR meta-analy*[ti] OR integrative review[tw] OR integrative research review[tw] OR rapid review[tw] OR umbrella review[tw] OR consensus development conference[pt] OR practice guideline[pt] OR drug class reviews[ti] OR cochrane database syst rev[ta] OR acp journal club[ta] OR health technol assess[ta] OR evid rep technol assess summ[ta] OR jbi database system rev implement rep[ta]) OR (clinical guideline[tw] AND management[tw]) OR ((evidence based[ti] OR evidence-based medicine[mh] OR best practice*[ti] OR evidence synthesis[tiab]) AND (review[pt] OR diseases category[mh] OR behavior and behavior mechanisms[mh] OR therapeutics[mh] OR evaluation study[pt] OR validation study[pt] OR guideline[pt] OR pmcbook)) OR ((systematic[tw] OR systematically[tw] OR critical[tiab] OR (study selection[tw]) OR (predetermined[tw] OR inclusion[tw] AND criteri* [tw]) OR exclusion criteri*[tw] OR main outcome measures[tw] OR standard of care[tw] OR standards of care[tw]) AND (survey[tiab] OR surveys[tiab] OR overview*[tw] OR review[tiab] OR reviews[tiab] OR search*[tw] OR handsearch[tw] OR analysis[ti] OR critique[tiab] OR appraisal[tw] OR (reduction[tw] AND (risk[mh] OR risk[tw]) AND (death OR recurrence))) AND (literature[tiab] OR articles[tiab] OR publications[tiab] OR publication [tiab] OR bibliography[tiab] OR bibliographies[tiab] OR published[tiab] OR pooled data[tw] OR unpublished[tw] OR citation[tw] OR citations[tw] OR database[tiab] OR internet[tiab] OR textbooks[tiab] OR references[tw] OR scales[tw] OR papers[tw] OR datasets[tw] OR trials[tiab] OR meta-analy*[tw] OR (clinical[tiab] AND studies[tiab]) OR treatment outcome[mh] OR treatment outcome[tw] OR pmcbook)) NOT (letter[pt] OR newspaper article[pt])) OR Technical Report[ptyp]) OR (((((trials[tiab] OR studies[tiab] OR database*[tiab] OR literature[tiab] OR publication*[tiab] OR Medline[tiab] OR Embase[tiab] OR Cochrane[tiab] OR Pubmed[tiab])) AND systematic*[tiab] AND (search*[tiab] OR research*[tiab]))) OR ((((((((((HTA[tiab]) OR technology assessment*[tiab]) OR technology report*[tiab]) OR (systematic*[tiab] AND review*[tiab])) OR (systematic*[tiab] AND overview*[tiab])) OR meta-analy*[tiab]) OR (meta[tiab] AND analyz*[tiab])) OR (meta[tiab] AND analys*[tiab])) OR (meta[tiab] AND analyt*[tiab]))) OR (((review*[tiab]) OR overview*[tiab]) AND ((evidence[tiab]) AND based[tiab]))))))
16	(#15) AND ("2015/06/01"[PDAT] : "3000"[PDAT])
17	(#16) NOT "The Cochrane database of systematic reviews"[Journal]
18	(#17) NOT (retracted publication [pt] OR retraction of publication [pt])

Leitlinien in Medline (PubMed) am 29.06.2020

#	**Suchfrage**
1	COVID-19 drug treatment[Supplementary Concept]
2	"COVID-19"[Supplementary Concept] OR "severe acute respiratory syndrome coronavirus 2"[Supplementary Concept]
3	Severe Acute Respiratory Syndrome [MeSH Terms]
4	"Pneumonia, Viral"[MeSH Major Topic]

5	(Viral[ti] OR virus*[ti]) AND (pneumonia*[ti] OR pneumonitis[ti] OR ((Lung*[ti] OR pulmonary[ti]) AND inflammation*[ti]))
6	"Severe Acute Respiratory Syndrome"[ti] OR SARS[ti] OR "severe acute respiratory infection"[ti] OR "severe acute respiratory infections"[ti] OR SARI[ti]
7	#1 OR #2 OR #3 OR #4 OR #5 OR #6
8	Coronavirus Infections[mh:noexp]
9	Coronavirus[MeSH Major Topic] OR SARS Virus[MeSH Major Topic]
10	Coronavirus[tiab] OR corona virus*[tiab]
11	Covid19[tiab] OR "Covid 19"[tiab] OR 2019ncov[tiab] OR 19ncov[tiab] OR cov2[tiab] OR ncov19[tiab] OR ncov2019[tiab] OR (ncov[tiab] AND 2019[tiab]) OR (ncov[tiab] AND 19[tiab])
12	(cov[tiab]) AND (novel[tiab] OR new[tiab] OR 2019[tiab] OR 19[tiab] OR infection*[tiab] OR disease*[tiab] OR wuhan[tiab] OR pneumonia*[tiab] OR pneumonitis[tiab] OR SARS[tiab] OR SARS2[tiab])
13	#8 OR #9 OR #10 OR #11 OR #12
14	(pneumonia*[tiab] OR pneumonitis[tiab] OR ((Lung*[tiab] OR pulmonary[tiab]) AND inflammation*[tiab]))
15	"Severe Acute Respiratory Syndrome"[tiab] OR SARS[tiab] OR "severe acute respiratory infection"[tiab] OR "severe acute respiratory infections"[tiab] OR SARI[tiab] OR "respiratory failure"[tiab] OR "respiratory distress"[tiab]
16	#14 OR #15
17	#13 AND #16
18	#7 OR #17
19	(#18) AND (Guideline[ptyp] OR Practice Guideline[ptyp] OR guideline*[Title] OR Consensus Development Conference[ptyp] OR Consensus Development Conference, NIH[ptyp] OR recommendation*[ti])
20	(#19) AND ("2015/06/01"[PDAT] : "3000"[PDAT])
21	(#20) NOT (retracted publication [pt] OR retraction of publication [pt])

Referenzen

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

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 24.07.2020

Indikation

Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der "*Behandlung von erwachsenen Patienten, die wegen einer schweren COVID-19 Lungenerkrankung/ Lungenentzündung im Krankenhaus behandelt werden*"? Wie sieht die Versorgungspraxis in Deutschland aus?

Etwa 80 % der Fälle mit einer COVID-19 Erkrankung verlaufen mild bis moderat und sind ambulant behandelbar. Bei etwa 20 % der Infizierten/Erkrankten kann es im Verlauf zu einer Verschlechterung meist innerhalb von 7–10 Tagen kommen mit klinischer Dyspnoesymptomatik und stationärer Behandlungspflichtigkeit. Eine solchermaßen schwere COVID-19 Lungenerkrankung bzw. Lungenentzündung ist klinisch gekennzeichnet durch pulmonale Infiltrate mit Gasaustauschstörung und Hypoxämie (SaO_2 < 90 %) sowie schwere Luftnotsymptomatik mit erhöhter Atemfrequenz und Fieber.

Der Behandlungsstandard in Deutschland (Stand Juli 2020) ist orientiert am klinischen Schweregrad und besteht in erster Linie aus supportiven Maßnahmen (1).

Hierzu zählt die Behandlung der Luftnot und Hypoxämie durch

- frühzeitige Sauerstoffgabe, sofern möglich bereits Bauchlagerung bei wachen Patienten („awake proning") ggf. auch high-flow Sauerstoff nasal und atemunterstützende Maßnahmen in Form nicht-invasiver Beatmung (NIV), bzw. auch invasiver Beatmung bis hin zum extrakorporalen Lungenersatzverfahren (ECMO) im Einzelfall.
- Des Weiteren je nach Vorliegen von Begleiterkrankungen bilanzierte Flüssigkeitstherapie, Thromboseprophylaxe aufgrund des erhöhten Thromboembolierisikos und bei Hinweisen auf eine bakterielle Superinfektion eine kalkulierte Antibiotikatherapie bzw. Sepsistherapie nach der aktuellen deutschen S3-Leitlinie (2), falls dies klinisch geboten erscheint.

Eine über diesen skizzierten supportiven Behandlungsstandard, der sich auch in der Versorgungspraxis etabliert hat, hinausgehende spezifische medikamentöse Therapie der Grunderkrankung ist bis dato in Deutschland nicht verfügbar gewesen.

Aufgrund einer Empfehlung des CHMP (Committee for Medicinal Products for Human Use) der Europäischen Arzneimittelbehörde (EMA) vom 25.6.2020 (3) erteilte die Europäische Kommission am 03.07.2020 eine bedingte Zulassung des Wirkstoffs Remdesivir (Veklury®) zur Behandlung von COVID-19 bei Erwachsenen und Jugendlichen ab 12 Jahren, die eine zusätzliche Sauerstoffgabe benötigen (4). Das Nukleotid-Analogon Remdesivir ist ein RNA-Polymerase-Inhibitor, der die Replikation von Coronaviren hemmen kann und ursprünglich zur Behandlung von Ebola-Infektionen entwickelt wurde. Die aktuelle EMA-Entscheidung zur bedingten Zulassung beruht im wesentlichen auf vorläufigen Ergebnissen einer von den National Institutes of Health (NIH) initiierten multizentrischen doppelblinden randomisierten Phase-III-Studie bei 1063 hospitalisierten COVID-19-Patienten (Adaptive COVID-19 Treatment Trial,

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 24.07.2020

Indikation

Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.

ACTT-1) (5). Patienten, die Remdesivir erhielten, hatten eine statistisch signifikant verkürzte mediane Zeit bis zur Genesung (recovery) im Median von 11 Tagen gegenüber der Placebogruppe mit 15 Tagen. In Subgruppenanalysen war der Effekt am deutlichsten bei Patienten, die Sauerstoff erhielten. Patienten, die beatmet wurden bzw. einen extrakorporalen Lungenersatz (ECMO) erhielten, profitierten nicht von der Therapie. Dies kann als Hinweis darauf gewertet werden, dass ein Therapieeffekt in fortgeschritteneren Stadien der Erkrankung nicht mehr besteht und daher ein frühzeitiger Einsatz eher anzustreben ist. Bezüglich der Mortalität war diese in der Remdesivir-Gruppe tendenziell geringer nach 14 Tagen mit 7,1 % vs. 11,9 % in der Placebo-Gruppe. Dieser Unterschied war aber statistisch nicht signifikant (p = 0,059).

Nach Ansicht der EMA überwiegt der Nutzen der sofortigen Verfügbarkeit von Remdesivir die potenziellen Risiken, die aus den noch nicht vorliegenden vollständigen klinischen Daten resultieren könnten. Der pharmazeutische Unternehmer ist verpflichtet bis Dezember 2020 Abschlussberichte seiner Studien vorzulegen. Weitere Daten zur Wirksamkeit und Sicherheit müssen gesammelt und regelmäßig überprüft werden (6).

Laut einer Oxford-Studie (RECOVERY-Study) kann eine niedrig-dosierte Behandlung mit dem Steroid Dexamethason die Sterblichkeitsrate schwer erkrankter COVID-19-Patienten deutlich senken (7):

- Mehr als 11.500 Patienten, die seit März 2020 an 175 Kliniken des britischen Gesundheitsdienstes (NHS) wegen COVID-19 behandelt wurden, erhielten Dexamethason.
- Ohne Behandlung mit Dexamethason lag die Sterblichkeitsrate bei Patienten, die klinisch beatmet werden mussten, bei 41 %. Von Menschen, die Sauerstoff erhielten, aber selbst atmen konnten, starben 25 %. Und bei Patienten, die nicht mit zusätzlichem Sauerstoff versorgt wurden, lag die Sterblichkeitsrate bei 13 %.
- Dexamethason wirkt entzündungshemmend und hilft, wenn es zu einer übermäßigen Reaktion des Immunsystems, die auch bei schweren Verläufen von COVID-19-Patienten auftritt (1).

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*einer schweren COVID-19 Lungenerkrankung bzw. Lungenentzündung*“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Ein Kriterium einer Behandlungsentscheidung stellt der Zeitpunkt der Erkrankung dar, d. h. dass in der Frühphase der Erkrankung (etwa bis 10 Tage nach Symptombeginn) eher ein Nutzen einer antiviral wirksamen Medikation zu erwarten ist als in der Spätphase der Erkrankung, die durch eine Hyperinflammation gekennzeichnet ist. Ergänzend bzw. darüber hinaus als weiteres Kriterium das Ausmaß der Gasaustauschstörung und der dadurch notwendigen Sauerstoff- bzw. apparativen Therapienotwendigkeit ergibt. So zeigen die vorläufigen Ergebnisse der ACTT-1-Studie, dass in den Subgruppenanalysen beatmungspflichtige Patienten keinen Vorteil einer Remdesivir-Behandlung erfahren. (5)

Der pU plant folgende spezielle Patientenpopulation zu untersuchen:

Patienten mit einer COVID-19 Erkrankung mit einer Pneumonie mit Bedarf an zusätzlicher Sauerstoffversorgung

Kontaktdaten

Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 24.07.2020

Indikation

Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.

Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Bei Vorliegen einer COVID-19-Pneumonie mit Sauerstoffpflichtigkeit sollte die Therapie mit Remdesivir möglichst frühzeitig eingeleitet werden. Bei Patienten unter nicht-invasiver oder invasiver Beatmungstherapie inkl. ECMO wurde kein Nutzen gezeigt.

Eine Therapie mit Dexamethason bei Patienten mit invasiver Beatmung oder Sauerstoff-Therapie mit einer Krankheitsdauer von mindestens sieben Tagen kann indiziert sein. Bei Patienten ohne Atmungsunterstützung besteht weiterhin keine Indikation einer Therapie mit Dexamethason, nach den Auswertungen der RECOVERY-Studie könnte sogar die Mortalität erhöht sein.

((1): siehe Grafik 1, Seite 12), (5;7)

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Kontaktdaten Arzneimittelkommission der deutschen Ärzteschaft (AkdÄ), Herbert-Lewin-Platz 1, 10623 Berlin (www.akdae.de); Stand: 24.07.2020
Indikation Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.
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Beteiligung von AkdÄ und Fachgesellschaften nach §35a Abs. 7 SGB V i.V.m. VerfO 5. Kapitel § 7 Abs. 6

Kontaktdaten

Deutsche Gesellschaft für Internistische Intensiv und Notfallmedizin.

Abgestimmt mit: Deutsche Gesellschaft für Pneumologie.

Indikation

Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.

Was ist der Behandlungsstandard unter Berücksichtigung der vorliegenden Evidenz bei der "*Behandlung von erwachsenen Patienten, die wegen einer schweren COVID-19 Lungenerkrankung/ Lungenentzündung im Krankenhaus behandelt werden***"? Wie sieht die Versorgungspraxis in Deutschland aus?**

Zur Versorgungspraxis: Demographie der Patienten mit COVID-19: 52% weiblich, 48% männlich, Altersdurchschnitt 48 Jahre. Dauer des Krankenhausaufenthaltes im Mittel 10 Tage. Etwa 83% der Erkrankungen verlaufen mild bis moderat. Bei 17 % erfolgt eine stationäre Aufnahme wg. Dyspnoe, und/oder Hypoxämie, typischerweise ca. 7-10 Tage nach Symptombeginn. Bei ca. 5% der Patienten besteht eine Indikation zur intensivmedizinischen Therapie.

Klinische Klassifikation nach Schweregrad:

- Leicht und unkompliziert (keine Pneumonie)
- Moderat (leichte Pneumonie)
- Schwer (Pneumonie, definiert durch Fieber und beidseitige Lungeninfiltrate und entweder Atemfrequenz > 30/min, schwere Luftnot oder SpO2 <90% bei Raumluft)
- Kritisch (ARDS, Hyperinflammation mit dem klinischen Bild einer Sepsis, bzw. eines septischen Schocks mit Multiorganversagen)

Behandlungsstandard bei erwachsenen Patienten im Krankenhaus:

- Restriktive Flüssigkeitstherapie
- Ernährungsoptimierung
- Engmaschige Überwachung der Vitalparameter
- Konsequente Einleitung einer Thromboseprophylaxe, ggf. therapeutische Antikoagulation
- Sauerstoffgabe nach Bedarf, Ziel SpO2 > 90%
- Kontrolle der Entzündungsparameter (CRP, IL-6), Nierenfunktion, Leberwerte, Gerinnung (inkl. D-Dimer)
- Bildgebung je nach klinischem Verlauf
- Ko-Infektionen/ Sekundärinfektionen berücksichtigen
- Mikrobiologische Diagnostik je nach klinischem Verlauf

Kontaktdaten

Deutsche Gesellschaft für Internistische Intensiv und Notfallmedizin.

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Indikation

Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.

- Bei hypoxämischem respiratorischen Versagen erfolgt je nach Schweregrad eine Therapie mit Sauerstoff/Highflow-Sauerstofftherapie/nichtinvasiver Beatmung. Häufig ist dann eine mechanische Beatmung auch notwendig, als ultima ratio eine extrakorporale Membranoxygenierung (ECMO):

Gibt es Kriterien für unterschiedliche Behandlungsentscheidungen bei der Behandlung von „*einer schweren COVID-19 Lungenerkrankung bzw. Lungenentzündung*“ die regelhaft berücksichtigt werden? Wenn ja, welche sind dies und was sind in dem Fall die Therapieoptionen?

Medikamentöse Therapie:

Eine klinische Wirksamkeit einer medikamentösen Therapie bei schwerer COVID-Erkrankung (hospitalisierte Patienten) ist bisher für Remdesivir und Dexamethason nachgewiesen. Eine Zulassung von Remdesivir erfolgte am 03.07.2020 in Europa zur Behandlung von SARS-CoV-2 bedingten Pneumonien mit Sauerstoffbedarf. Ein Benefit für Remdesivir ist am besten ersichtlich bei Patienten die Sauerstoff benötigen, für beatmete Patienten liegen noch keine ausreichenden Daten vor. Demgegenüber zeigt eine Therapie mit Dexamethason einen Überlebensvorteil insbesondere bei beatmungspflichtigen Patienten mit COVID-19.

Andere Substanzen, sowohl mit antiviraler Wirksamkeit wie auch immunmodulatorische Therapien, können derzeit außerhalb klinischer Studien und entsprechend qualifizierter klinischer Einrichtungen nicht zum Einsatz empfohlen werden.

S1-Leitlinie Empfehlungen zur intensivmedizinischen Therapie von Patienten mit COVID-19. Stand 21.07.2020 (Version 3). AWMF-Register-Nr. 113/001

https://www.awmf.org/uploads/tx_szleitlinien/113-001l_S1_Intensivmedizinische-Therapie-von-Patienten-mit-COVID-19_2020-07.pdf

Zu den generellen Maßnahmen bei akuter hypoxämischer respiratorischer Insuffizienz verweisen wir auf die obengenannte Leitlinie und das Positionspapier zur praktischen Umsetzung der apparativen Differenzialtherapie der akuten respiratorischen Insuffizienz bei COVID-19 der Deutsche Gesellschaft für Pneumologie und Beatmungsmedizin e.V. (DGP).

https://www.thieme-connect.de/products/ejournals/html/10.1055/a-1157-9976

Der pU plant folgende spezielle Patientenpopulation zu untersuchen:

Patienten mit einer COVID-19 Erkrankung mit einer Pneumonie mit Bedarf an zusätzlicher Sauerstoffversorgung

Ergibt sich bei Berücksichtigung dieser Patientencharakteristika bzw. der beschriebenen Behandlungssituation eine andere Vergleichstherapie?

Kontaktdaten *Deutsche Gesellschaft für Internistische Intensiv und Notfallmedizin.* *Abgestimmt mit: Deutsche Gesellschaft für Pneumologie.*
Indikation Behandlung von erwachsenen Patienten und Jugendlichen ab 12 Jahren, die wegen einer schweren COVID-19 Lungenerkrankung im Krankenhaus behandelt werden.
Bitte siehe oben. Bitte begründen Sie Ihre Ausführungen *(hier ergänzen – sofern verfügbar – auf welcher (Daten-)Grundlage basiert die Einschätzung; ggf. beifügen der zitierten Quellen)*