Special Article

Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)

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Background: The novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a rapidly spreading illness, Coronavirus Disease 2019 (COVID-19), affecting thousands of people around the world. Urgent guidance for clinicians caring for the sickest of these patients is needed.
Methods: We formed a panel of 36 experts from 12 countries. All panel members completed the World Health Organization conflict of interest disclosure form. The panel proposed 53 questions that are relevant to the management of COVID-19 in the ICU. We searched the literature for direct and indirect evidence on the management of COVID-19 in critically ill patients in the ICU. We identified relevant and recent systematic reviews on most questions relating to supportive care. We assessed the certainty in the evidence using the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach, then generated recommendations based on the balance between benefit and harm, resource and cost implications, equity, and feasibility. Recommendations were either strong or weak, or in the form of best practice recommendations.
Results: The Surviving Sepsis Campaign COVID-19 panel issued 54 statements, of which four are best practice statements, nine are strong recommendations, and 35 are weak recommendations. No recommendation was provided for six questions. The topics were: 1) infection control, 2) laboratory diagnosis and specimens, 3) hemodynamic support, 4) ventilatory support, and 5) COVID-19 therapy.
Conclusion: The Surviving Sepsis Campaign COVID-19 panel issued several recommendations to help support healthcare workers caring for critically ill ICU patients with COVID-19. When available, we will provide new evidence in further releases of these guidelines. (*Crit Care Med* 2020; XXX:00–00)

INTRODUCTION

At the end of 2019, a novel coronavirus, named severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), resulted in an acute respiratory illness epidemic in Wuhan, China (1). The World Health Organization (WHO) termed this illness Coronavirus Disease 2019 (COVID-19).

By the time this guideline panel was assembled, the COVID-19 had become a pandemic and had affected over 120,000 individuals in more than 80 countries, and resulted in more than 5000 deaths worldwide (2).

The WHO and the United States Center for Disease Control and Prevention (CDC) have issued preliminary guidance on infection control, screening and diagnosis in the general population, but there is limited guidance on the acute management of critically ill patients with severe illness due to COVID-19.

Guideline Scope

This guideline provides recommendations to support hospital clinicians managing critically ill adults with COVID-19 in the intensive care unit (ICU). The target users of this guideline are frontline clinicians, allied health professionals, and policymakers involved in the care of patients with COVID-19 in the ICU. The guideline applies to both high and low-middle income settings.

Guideline Teams and Structure

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.

The SSC COVID-19 panel was assembled and worked within very tight timelines in order to issue recommendations in a timely manner. The panel included experts in guideline development, infection control, infectious diseases and microbiology, critical care, emergency medicine, nursing, and public health. The panel was divided into four groups: 1) infection control and testing, 2) hemodynamic support, 3) ventilatory support, and 4) therapy.

The *Guidelines in Intensive Care Development and Evaluation* (GUIDE) group provided methodological support throughout the guideline development process.

Management of Conflict of Interests

All panel members completed a conflict of interests (COI) form prior to joining the guideline panel (3, 4). We used the GRADEpro guideline development tool (GDT) online software (http://gdt.guidelinedevelopment.org) to administer WHO COI disclosure forms to participating panel members. Direct financial and industry-related COIs were not permitted and were considered disqualifying. The development of this guideline did not include any industry input, funding, or financial or non-financial contribution. No member of the guideline panel received honoraria or remuneration for any role in the guideline development process.

METHODS

The guideline development process is summarized in **Figure 1**. All actionable guideline questions were structured in the Population, Intervention, Control, and Outcome(s) (PICO) format, with explicit definitions, whereas descriptive questions were not.

Content and methods experts in each group participated in developing the guideline questions. The PICO format provided the basis for defining inclusion and exclusion criteria for the literature searches (where performed) and for identification of relevant studies.

To facilitate rapid development of recommendations, we did not perform a novel systematic prioritization of outcomes, but used the outcome prioritization informed by the ongoing SSC guideline 2020 work and expert input (5). Accordingly, we focused on hospital mortality and serious adverse event outcomes for most questions, and for some included other outcomes deemed critical for decision making.

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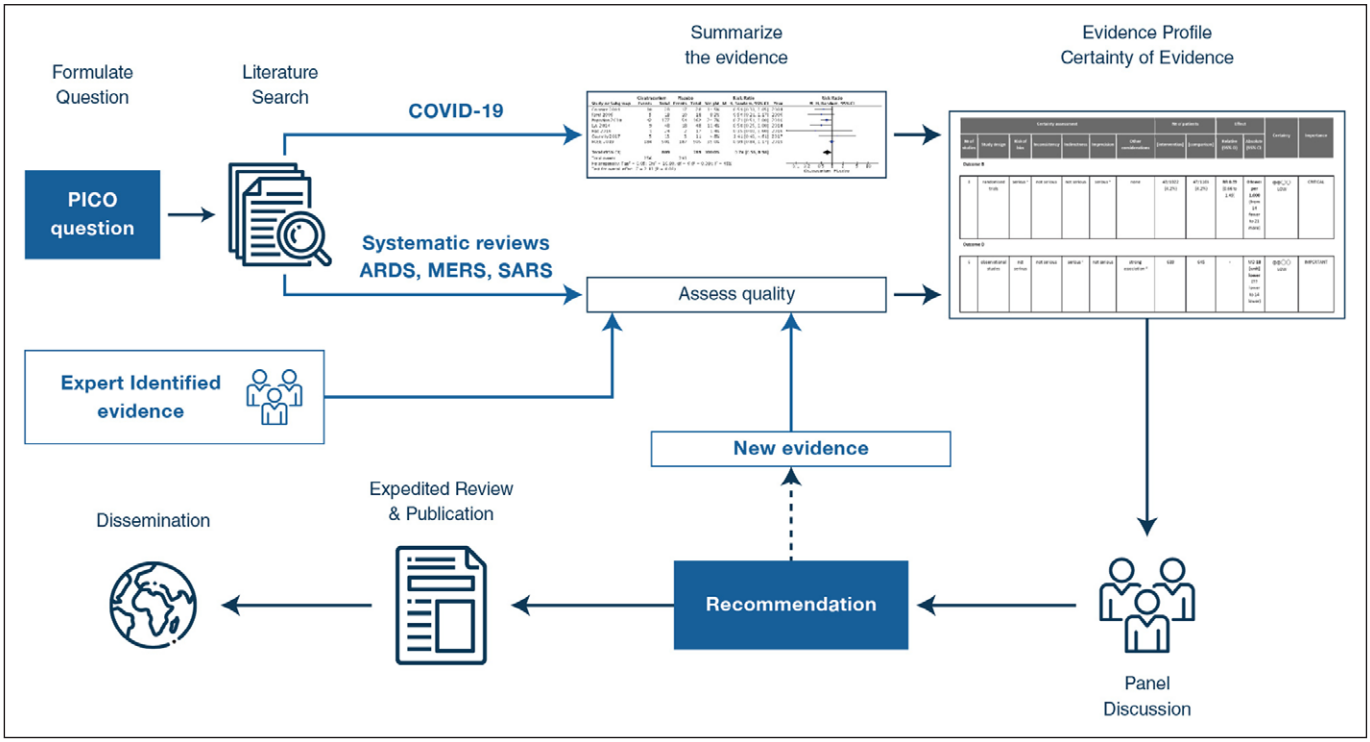

Figure 1. COVID-19 guideline development process.

Literature Search

For some questions, with help of professional medical librarians, 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. To inform the recommendations on hemodynamic and ventilatory support, we used recently published systematic reviews and asked experts to identify any new relevant studies.

Selection of Studies and Data Abstraction

For selected PICO questions, a pair of reviewers screened titles and abstracts retrieved from the bibliographic databases; for each PICO question, all potentially eligible studies were assessed for eligibility according to pre-specified criteria. Content experts were asked to indicate any additional studies not identified by the search. Subsequently, pairs of reviewers independently abstracted relevant data on the corresponding PICO questions, and items relevant to risk of bias. We obtained intention-to-treat data whenever available; otherwise we used complete case data (i.e., ignoring missing data) (6).

Quality of Evidence

We used the *Grading of Recommendations, Assessment, Development and Evaluation* (GRADE) approach to assess the quality of evidence (7), (i.e., our confidence in the estimate of the effect to support a recommendation) (8). The quality of evidence was rated as high, moderate, low, or very low (9). We used the GDT online software (http://gdt.guidelinedevelopment.org) to generate the evidence profiles (evidence summaries) (10).

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 (**Figs. S1** and **S2**, Supplemental Digital Content 1, http://links.lww.com/CCM/F457).

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 (**Fig. S3**, Supplemental Digital Content 1, http://links.lww.com/CCM/F457). 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.

RECOMMENDATION FORMULATION

We used the principles outlined in the evidence to decision framework (EtD) to formulate recommendations, but because of the tight timelines we did not complete the online EtD tables (11). The EtD framework covers the following domains: priority setting, magnitude of benefit and harm, certainty of the evidence, patient values, balance between desirable and undesirable effects, resources and cost, equity, acceptability and feasibility.

Each of the four subgroups drafted the preliminary recommendations. We use the wording "we recommend" for strong recommendations and "we suggest" for suggestions (i.e., weak recommendations). The implications of the recommendation

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TABLE 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

strength are presented in **Table 1**. The final list of recommendations was developed by panel discussion and consensus; voting on recommendations was not required. We present the guideline statements and recommendations in **Table 2**.

Updating the Recommendations

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.

I. INFECTION CONTROL

Risk of SARS-CoV-2 Transmission

A recent report from the Chinese Center of Disease Control and Prevention described 72,314 cases of COVID-19 from China, of which 44,672 were laboratory confirmed. Among laboratory-confirmed cases, 1,716 (3.8%) were healthcare workers, most of whom, 63% (1,080 of 1,716), acquired the infection in Wuhan. The report describes that 14.8% (247 of 1668) of infected healthcare workers had severe or critical illness, and that five died (12). In Italy, as of March 15, 2020, there are 2,026 documented COVID-19 cases among healthcare workers (13). Although incidence data are not available, these data point to a considerable burden of infection among healthcare workers. The risk of patient-to-patient transmission in the ICU is currently unknown, therefore, adherence to infection control precautions is paramount.

Healthcare workers should follow the infection control policies and procedures already in place at their healthcare institutions. We provide the following recommendations and suggestions as considerations rather than a requirement to change institutional infection control policies.

Recommendation:

1. For healthcare workers performing **aerosol-generating procedures*** on patients with COVID-19 in the ICU, we ***recommend*** using **fitted respirator masks** (**N95 respirators, FFP2, or equivalent**), as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (best practice statement).

Rationale:

Respirator masks are designed to block 95% to 99% of aerosol particles. The N95 type conforms to United States Federal Drug Agency standards, and the FFP2 conforms to European standards–European Committee for Standards standards). Staff should be fit tested for each different type. Surgical masks (also known as medical masks) are designed to block large particles, droplets and sprays, but are less effective in blocking small particle aerosols (< 5 µm) (14).

This recommendation is based on a consensus of recommendations from the CDC, WHO, and other public health organizations, along with epidemiologic data demonstrating that aerosol-generating procedures increased risk to healthcare workers during the SARS epidemic. Powered air purifying respirators (PAPRs) can be used by healthcare workers who failed N95 mask fit testing and when N95s are in limited supply.

Recommendation:

2. We ***recommend*** performing **aerosol-generating procedures** on ICU patients with COVID-19 in a negative pressure room (best practice statement).

Rationale:

Negative pressure rooms are an engineering control intended to prevent the spread of contagious airborne pathogens from

*Aerosol-generating procedures in the ICU include endotracheal intubation, bronchoscopy, open suctioning, administration of nebulized treatment, manual ventilation before intubation, physical proning of the patient, disconnecting the patient from the ventilator, non-invasive positive pressure ventilation, tracheostomy, and cardiopulmonary resuscitation.

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TABLE 2. Recommendations and Statements

	Recommendation	Strength
Infection Control and Testing:		
1	For healthcare workers performing **aerosol-generating procedures*** on patients with COVID-19 in the ICU, we ***recommend*** using **fitted respirator masks (N95 respirators, FFP2, or equivalent)**, as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles)	Best practice statement
2	We ***recommend*** performing **aerosol-generating procedures** on ICU patients with COVID-19 in a negative pressure room.	Best practice statement
3	For healthcare workers providing usual care for non-ventilated COVID-19 patients, we ***suggest*** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles).	Weak
4	For healthcare workers who are performing **non-aerosol-generating procedures** on mechanically ventilated (closed circuit) patients with COVID-19, we ***suggest*** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles).	Weak
5	For healthcare workers performing **endotracheal intubation** on patients with COVID-19, we ***suggest*** using video-guided laryngoscopy, over direct laryngoscopy, if available.	Weak
6	For COVID-19 patients requiring **endotracheal intubation**, we ***recommend*** that endotracheal intubation be performed by the healthcare worker who is most experienced with airway management in order to minimize the number of attempts and risk of transmission.	Best practice statement
7.1	For intubated and mechanically ventilated adults with suspicion of COVID-19: For diagnostic testing, we ***suggest*** obtaining lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal) samples.	Weak
7.2	For intubated and mechanically ventilated adults with suspicion of COVID-19: With regard to lower respiratory samples, we ***suggest*** obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples.	Weak
Hemodynamics:		
8	In adults with **COVID-19 and shock**, we ***suggest*** using dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness.	Weak
9	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest*** using a conservative over a liberal fluid strategy.	Weak
10	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***recommend*** using crystalloids over colloids.	Weak
11	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest*** using buffered/balanced crystalloids over unbalanced crystalloids.	Weak
12	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***recommend against*** using hydroxyethyl starches.	Strong
13	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** using gelatins.	Weak
14	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** using dextrans.	Weak
15	For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** the routine use of albumin for initial resuscitation.	Weak
16	For adults with **COVID-19 and shock**, we ***suggest*** using norepinephrine as the first-line vasoactive agent, over other agents.	Weak
17	If norepinephrine is not available, we ***suggest*** using either vasopressin or epinephrine as the first-line vasoactive agent, over other vasoactive agents, for adults with **COVID-19 and shock.**	Weak
18	For adults with **COVID-19 and shock**, we ***recommend against*** using dopamine if norepinephrine is available.	Strong

(*Continued*)

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TABLE 2. (*Continued*). Recommendations and Statements

	Recommendation	Strength
19	For adults with **COVID-19 and shock**, we ***suggest*** adding vasopressin as a second-line agent, over titrating norepinephrine dose, if target mean arterial pressure (MAP) cannot be achieved by norepinephrine alone.	Weak
20	For adults with **COVID-19 and shock**, we ***suggest titrating*** vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets.	Weak
21	For adults with **COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine**, we ***suggest*** adding dobutamine, over increasing norepinephrine dose.	Weak
22	For adults with **COVID-19 and refractory shock**, we ***suggest*** using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid. **Remark**: A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.	Weak
Ventilation:		
23	In adults with COVID-19, we ***suggest*** starting supplemental oxygen if the peripheral oxygen saturation (Spo_2) is < 92%, and ***recommend*** starting supplemental oxygen if Spo_2 is < 90%	Weak Strong
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
25	For adults with COVID-19 and **acute hypoxemic respiratory failure** despite conventional oxygen therapy, we ***suggest*** using HFNC over conventional oxygen therapy.	Weak
26	In adults with COVID-19 and **acute hypoxemic respiratory failure**, we ***suggest*** using HFNC over NIPPV.	Weak
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 NIPPV with close monitoring and short-interval assessment for worsening of respiratory failure.	Weak
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.	No recommendation
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
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
31	For mechanically ventilated adults with COVID-19 and **ARDS**, we ***recommend*** targeting plateau pressures (Pplat) of < 30 cm H_2O.	Strong
32	For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we ***suggest*** using a higher PEEP strategy, over a lower PEEP strategy. **Remarks**: If using a higher PEEP strategy (i.e., PEEP > 10 cm H_2O), clinicians should monitor patients for barotrauma.	Strong
33	For mechanically ventilated adults with COVID-19 and ARDS, we ***suggest*** using a conservative fluid strategy over a liberal fluid strategy.	Weak
34	For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we ***suggest*** prone ventilation for **12 to 16 hours**, over no prone ventilation.	Weak
35.1	For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we ***suggest*** using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA), over continuous NMBA infusion, to facilitate protective lung ventilation.	Weak
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 hours.	Weak
36	In mechanically ventilated adults with COVID-19 ARDS, we ***recommend against*** the routine use of inhaled nitric oxide.	Weak

(*Continued*)

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TABLE 2. (*Continued*). Recommendations and Statements

	Recommendation	Strength
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 rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off.	Weak
38	For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, we ***suggest*** using recruitment maneuvers, over not using recruitment maneuvers.	Weak
39	If recruitment maneuvers are used, we ***recommend against*** using staircase (incremental PEEP) recruitment maneuvers.	Strong
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) ECMO if available, or referring the patient to an ECMO center. **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.	Weak
	Therapy:	
41	In mechanically ventilated adults with COVID-19 and respiratory failure (**without ARDS**), we ***suggest against*** the routine use of systemic corticosteroids.	Weak
42	In mechanically ventilated adults with COVID-19 **and ARDS**, we ***suggest*** using systemic corticosteroids, over not using corticosteroids. **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.	Weak
43	In mechanically ventilated patients with COVID-19 and respiratory failure, we ***suggest*** using empiric antimicrobials/antibacterial agents, over no antimicrobials. **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.	Weak
44	For critically ill adults with COVID-19 who develop fever, we ***suggest*** using acetaminophen/paracetamol for temperature control, over no treatment.	Weak
45	In critically ill adults with COVID-19, we ***suggest against*** the routine use of standard intravenous immunoglobulins (IVIG).	Weak
46	In critically ill adults with COVID-19, we ***suggest against*** the routine use of convalescent plasma.	Weak
47.1	In critically ill adults with COVID-19: we ***suggest against*** the routine use of lopinavir/ritonavir.	Weak
47.2	**There is insufficient evidence to issue a recommendation** on the use of other antiviral agents in critically ill adults with COVID-19.	No 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.	No recommendation
49	**There is insufficient evidence to issue a recommendation** on the use of chloroquine or hydroxychloroquine in critically ill adults with COVID-19.	No recommendation
50	**There is insufficient evidence to issue a recommendation** on the use of tocilizumab in critically ill adults with COVID-19.	No recommendation

room to room (e.g. measles, and tuberculosis). The main goal is to avoid the accidental release of pathogens into a larger space and open facility, thereby protecting healthcare workers and patients in a hospital setting. Negative air pressure is created in the patient's room to keep the pathogen inside and avoid its diffusion. By adopting this precaution when aerosol-generating procedures like tracheal intubation, bronchoscopies, or non-invasive positive pressure ventilation (NIPPV) are performed within the room, there is a lower risk of cross-contamination among rooms and infection for staff and patients outside the room. Negative pressure is created and maintained by a ventilation system that allows extra air to enter the isolated room by differential pressure and be exhausted directly to the outside or be filtered through a high-efficiency particulate air (HEPA) filter directly before recirculation. Moreover, the presence of unnecessary staff in the room should be avoided.

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Negative pressure rooms have proven to be an effective measure that helped to avoid cross-contamination during the SARS epidemic (15). Accordingly, for aerosol-generating procedures, the WHO guidance on COVID-19 recommends the use of negative pressure rooms with a minimum of 12 air changes per hour or at least 160 L/sec/patient in facilities with natural ventilation (16). Bronchoscopies are among the procedures at highest risk of aerosolization, and their use should be minimized. Non-invasive ventilation is also at high risk of aerosolization, and strategies have been described to contain the risk (17) of virus spread, also according to a previous report on SARS infection (18).

Where this is not feasible, a portable HEPA filter should be used in the room wherever possible. A HEPA filter is a mechanical air filter, used for isolation where maximum reduction or removal of submicron particulate matter from air is required. HEPA filters have been demonstrated to reduce virus transmission in simulated settings (19).

Recommendations:

3. For healthcare workers providing usual care for non-ventilated COVID-19 patients, we ***suggest*** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low-quality evidence).
4. For healthcare workers who are performing **non-aerosol-generating procedures** on mechanically ventilated (closed circuit) patients with COVID-19, we ***suggest*** using surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles) (weak recommendation, low-quality evidence).

Rationale:

Our recommendations are in line with the WHO guidance, and with the current evidence, which suggests that surgical/medical masks are probably not inferior to N95 respirators for providing protection against laboratory confirmed seasonal respiratory viral infections (e.g., influenza, but not measles). We updated the most recent systematic review and meta-analysis of RCTs (20), and identified one new RCT (21). Overall, four RCTs (5,549 individuals) randomized healthcare workers to N95 respirators or medical masks (21–25). The use of medical masks, as opposed to N95 respirators, did not increase laboratory-confirmed respiratory infection (OR, 1.06; 95% CI, 0.90 to 1.25). Although the point estimates suggest that use of medical masks was associated with increased risk of influenza-like illness (OR, 1.31; 95% CI, 0.94, 1.85) and clinical respiratory infection (OR, 1.49; 95% CI, 0.98 to 2.28), the differences were not statistically significant. A recent systematic review and meta-analysis reached similar conclusions (26).

Only one RCT reported on coronavirus. On testing for seasonal coronavirus (OC43, HKU1, 229E, NL63) by means of PCR in this non-cluster RCT, 4.3% (9 of 212) of nurses in the medical mask group had RT-PCR confirmed coronavirus infection as compared with 5.7% (12 of 210) in the N95 respirator group (22).

When making these recommendations, the panel considered the lack of convincing evidence that N95 respirators improve clinical outcomes, the cost and resources associated with N95 mask use, and the need to preserve the N95 respirator supply for aerosol-generating procedures. Therefore, the panel issued a suggestion to use medical masks in this context. However, SARS-CoV-2 appears to be more easily transmissible and lethal than seasonal influenza. Specifically, an early estimate of the reproductive number (R_0) of SARS-CoV-2, the average number of people an infected person subsequently infects as a function of biological properties of the pathogen in combination with social and environmental factors, is 2.3 (27). By comparison, the estimated average R_0 for the 1,918 influenza pandemic that resulted in an estimated 50 million deaths globally was 1.8, and the estimated average R_0 for seasonal influenza is 1.28 (28). Therefore, a minimum of a surgical/medical mask is recommended for healthcare workers caring for non-ventilated COVID-19 patients and for healthcare workers who are performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19. When scarcity is not an issue, use of a fitted respirator use of a fitted respirator mask is a reasonable option.

Recommendation:

5. For healthcare workers performing **endotracheal intubation** on patients with COVID-19, we ***suggest*** using video-guided laryngoscopy, over direct laryngoscopy, if available (weak recommendation, low-quality evidence).

Rationale:

There is no direct evidence comparing the use of video-laryngoscopy with direct laryngoscopy for intubation of patients with COVID-19. While SARS-CoV-2 appears to be predominantly spread by large respiratory droplets, intubation is likely a small particle (less than 5 µm) aerosol-generating procedure, which increases the risk of transmission to healthcare workers (29). Intubation is particularly risky given the close contact of healthcare workers with the patient's airway and respiratory secretions. Thus, techniques that can reduce the number of attempts at endotracheal intubation and the duration of the procedure and minimize the proximity between the operator and the patient, should be prioritized, potentially reducing the risk of complications in hypoxic COVID-19 patients. In a systematic review including 64 studies and 7,044 patients, video-laryngoscopy reduced the risk of failed intubation (OR, 0.35; 95% CI, 0.19 to 0.65), without a significant impact upon the proportion of successful first-pass attempts (OR, 0.79; 95% CI, 0.48 to 1.3), hypoxia (OR, 0.39; 95% CI, 0.1 to 1.44), or time for tracheal intubation (30, 31). In patients with difficult airways, the first-attempt success rate may be improved with video-laryngoscopy (32).

Thus, in settings where video-laryngoscopy is available and staff are skilled in its use, we suggest that it be used, in preference to direct laryngoscopy, to maximize the chances of

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success. Recognizing that not all centers will have rapid access to video-laryngoscopy or skilled users, this recommendation is conditional.

Recommendation:

6. For COVID-19 patients requiring **endotracheal intubation**, we ***recommend*** that endotracheal intubation be performed by the healthcare worker who is most experienced with airway management in order to minimize the number of attempts and risk of transmission (best practice statement).

Rationale:

Similar to the reasoning above, factors that maximize the chances of first pass success should be used when intubating patients with suspected or confirmed COVID-19. Thus, we recommend that the healthcare operator with the most experience and skill in airway management should be the first to attempt intubation.

II. LABORATORY DIAGNOSIS AND SPECIMENS

Indications for Testing ICU Patients for SARS-CoV-2

The WHO recently declared a COVID-19 pandemic. Accordingly, every critically ill patient arriving with evidence of respiratory infection should be considered potentially infected with SARS-CoV-2. Real-time polymerase chain reaction (RT-PCR) is the gold standard for similar viral infections, including SARS (33). Notably, COVID-19 poses several diagnostic challenges due to an extended incubation period (approximately two weeks) that includes a prolonged interval (approximately 5 days) of viral shedding prior to the onset of symptoms. Moreover, the duration of asymptomatic shedding is not only variable but may also differ based on the anatomic level (upper versus lower) of the infection in the respiratory system (1, 34). Accordingly, the performance of biomolecular assay may vary by site of sampling.

Recommendations:

7. For intubated and mechanically ventilated adults with suspicion of COVID-19:

7.1. For diagnostic testing, we ***suggest*** obtaining lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal) samples (weak recommendation, low-quality evidence).

7.2. With regard to lower respiratory samples, we ***suggest*** obtaining endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples (weak recommendation, low-quality evidence).

Rationale:

COVID-19 diagnosis is based on RT-PCR testing of respiratory samples from nasopharyngeal and oropharyngeal swabs, and of lower respiratory tract samples whenever possible. Bronchoalveolar lavage should be limited and performed only if indicated and with adequate precautions, due to the risk of aerosolization and consequent exposure of healthcare professionals. Similarly, sputum induction should be avoided due to increased risk of aerosolization. Tracheal aspirate specimens appear to carry a lower risk of aerosolization and can sometimes be obtained without disconnecting the patient from the ventilator.

The procedures involved in laboratory RT-PCR testing for SARS-CoV-2 using a number of assays currently in use are well described (35). Despite the generally high sensitivity and specificity of RT-PCR-based assays (36), it may not be enough to rely on oropharyngeal swabs specimens alone for SARS-CoV-2 diagnosis due to their low negative predictive value. In a recent study, only 9 out of 19 (47%) oropharyngeal swabs from COVID-19 patients tested positive by RT-PCR (37). Similar data were reported using RT-PCR during the 2002–2003 SARS epidemic (38). Using seroconversion as the "gold standard" for SARS diagnosis, RT-PCR assays performed on nasopharyngeal and throat specimens were positive only 65% and 70% of the time, respectively. However, no false positives were observed indicating assay specificity of 100%. Similarly, in a study accounting for CT scan findings among suspected COVID-19 cases, 48% with negative oropharyngeal or nasal swabs were considered highly likely cases, and 33% were considered probable cases (39). Consequently, a single negative swab from the upper airway does not rule out SARS-CoV-2 infection and repeated sampling from multiple sites, including the lower airway, will increase diagnostic yield. Similarly, given that coinfection with other viral pathogens has been observed, a positive test for another respiratory virus does not rule out COVID-19, and should not delay testing if there is a high suspicion of COVID-19 (40). Given this high specificity, a single positive swab confirms the diagnosis of COVID-19 and is enough to trigger infection control precautions and appropriate treatment of the patient.

Lower respiratory tract specimens are considered to give a higher diagnostic yield than upper respiratory specimens in patients with pneumonia, consistent with what was observed for SARS (41), and should therefore be obtained whenever possible.

III. SUPPORTIVE CARE

A) Hemodynamic Support

Shock and Cardiac Injury in COVID-19 Patients. The reported prevalence of shock in adult patients with COVID-19 is highly variable (from 1% to 35%), depending on the patient population studied, the severity of illness, and the definition of shock. In a recent report summarizing the epidemiological characteristics of 44,415 Chinese patients with COVID-19, 2087 (5%) were diagnosed as critical cases, defined as severe hypoxemia and/or the presence of other organ failure, including shock (12). In another Chinese study of 1099 patients with COVID-19 with similar severity of illness, only 12 (1.1%) developed shock (1). In hospitalized patients, the incidence is likely higher (42) (**Table 3**), and may reach 20%–35% among patients in the ICU (42, 43).

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TABLE 3. Epidemiological Characteristics in Recent COVID-19 Reports

Study	n	ICU admission	Cardiac Injury	Shock	NIPPV	Invasive MV	CFR
Huang et al (44)	41	32%	12%	7%	24%	5%	15%
Chen et al (65)	99	23%	-	4%	13%	4%	11%
Wang et al (43)	138	26%	7%	9%	11%	12%	-
Guan et al (1)	1099	-	-	1%	5.1%	2.3%	1%
Yang et al (42)	52	100%	23%	35%	55.8%	42.3%	62%
Zhou et al (45)	191	26%	17%	20%	14%	17%	28%

CFR, case fatality rate; NIPPV, noninvasive positive pressure ventilation

Cardiac injury (elevation of cardiac injury biomarkers above the 99th percentile upper reference limit) has been reported in 7% to 23% of patients with COVID-19 in Wuhan, China (42–45). While the prevalence of cardiac injury may correlate with the prevalence of shock, a lack of systematic screening for cardiac dysfunction in hemodynamically stable patients means that this association cannot be taken as certain (**Table 3**).

The prognosis of patients with COVID-19 and shock has not been systematically reported. In a study of 150 patients from 2 hospitals in Wuhan, China, shock was a major reason for death in 40%, and may, at least in part, be due to fulminant myocarditis (46).

Studies on risk factors associated with shock in patients with COVID-19 are lacking. The majority of those that are available report unadjusted estimates (12, 42, 46). Despite methodological limitations, these studies suggest that older age, comorbidities (especially diabetes and cardiovascular disease including hypertension), lower lymphocyte count, higher D-dimer level, and possibly cardiac injury are risk factors to consider.

Fluid Therapy

Recommendation:

8. In adults with **COVID-19 and shock**, we ***suggest*** using dynamic parameters skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness (weak recommendation, low-quality evidence).

Rationale:

There is no direct evidence addressing the optimal resuscitation strategy in patients with COVID-19 and shock, therefore the panel based this recommendation on indirect evidence drawn from critically ill patients in general.

In a systematic review and meta-analysis of 13 RCTs (n = 1,652) examining the effect of dynamic assessment of fluid therapy on important patient outcomes in adult ICU patients requiring fluid resuscitation (47), the use of dynamic assessment to guide fluid therapy was found to reduce mortality (RR, 0.59; 95% CI, 0.42 to 0.83), ICU length of stay (MD, –1.16 days; 95% CI, –1.97 to –0.36) and duration of mechanical ventilation (−2.98 hours; 95% CI, −5.08 to −0.89). Of note, only one trial focused on patients with septic shock. Dynamic parameters used in these trials included stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume change with passive leg raising or fluid challenge. Among the examined dynamic parameters, passive leg raising followed by PPV and SVV appears to predict fluid responsiveness with highest accuracy (48). The static parameters included components of early goal-directed therapy, e.g., central venous pressure (CVP) and mean arterial pressure (MAP).

The use of serum lactate levels to guide resuscitation of patients with shock has been summarized in a systematic review and meta-analysis of seven RCTs (n = 1,301) (49). Compared with central venous oxygen saturation (ScVO2) guided therapy, early lactate clearance-directed therapy was associated with a reduction in mortality (RR, 0.68; 95% CI, 0.56 to 0.82), shorter ICU length of stay (MD, 1.64 days; 95% CI, −3.23 to −0.05), and shorter duration of mechanical ventilation (MD, −10.22 hours; 95% CI, −15.94 to −4.50). However, a high lactate level does not always indicate hypovolemia; it may also be caused by mitochondrial dysfunction, liver failure, beta-agonists, mesenteric ischemia, or epinephrine. In the ANDROMEDA-SHOCK trial, capillary refill testing (CRT) every 30 min was associated with a non-significant reduction in mortality (HR, 0.75; 95% CI, 0.55 to 1.02) compared with serum lactate measurement every 2 hours (50). CRT is a simple and easy test that can be used in almost any setting. Given the possible improvements in mortality, length of stay, and duration of mechanical ventilation that they may produce, as well as their availability, we suggest using dynamic parameters skin temperature, capillary refilling time, and/or lactate measurement over static parameters to assess fluid responsiveness in patients with COVID-19 and shock.

Recommendation:

9. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest*** using a conservative over a liberal fluid strategy (weak recommendation, very low-quality evidence).

Rationale:

No direct evidence exists on patients with COVID-19 and shock, therefore the panel used indirect evidence from critically ill patients with sepsis and ARDS to inform this recommendation.

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A recent systematic review of 9 RCTs (n = 637 patients) comparing restricted versus liberal fluid volumes in the initial resuscitation of patients with sepsis found no statistically significant difference in mortality (RR, 0.87; 95% CI, 0.69 to 1.10) and serious adverse events (RR, 0.91; 95% CI, 0.78 to 1.05) (51). However, all assessed outcomes favored conservative fluid therapy (lower volumes). Importantly, the quantity and quality of evidence were both judged to be very low, suggesting that more research is needed.

Correspondingly, in a 2017 meta-analysis of 11 RCTs (n = 2,051 patients), adults and children with ARDS or sepsis managed according to a conservative fluid strategy in the post-resuscitation phase of critical illness had more ventilator-free days and shorter ICU stays than patients managed according to a liberal fluid strategy (52) (see section on respiratory support for more details). In 2011, a large RCT of 3,141 febrile African children (FEAST) found that children randomized to fluid boluses with saline or albumin had increased mortality compared with children not receiving fluid boluses (53).

In the absence of data demonstrating a benefit of the use of liberal fluid strategies in critically ill patients with sepsis or ARDS, and considering that the majority of COVID-19 patients in the ICU develop ARDS, we suggest an initial conservative approach to fluid resuscitation in patients with COVID-19 and shock.

Recommendation:

10. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***recommend*** using crystalloids over colloids (strong recommendation, moderate quality evidence).

Rationale:

Since there exists no direct evidence on shock in patients with COVID-19, the panel based this recommendation on indirect evidence from critically ill patients in general.

In a systematic review of 69 RCTs (n = 30,020 patients) that compared the use of crystalloids versus colloids in critically ill patients (54), no outcomes favored the use of colloids. Considering that some colloids are harmful (see below), all colloids are more costly than crystalloids, and availability of colloids is limited in some settings (e.g., some low- and middle-income countries), we recommend using crystalloids for fluid resuscitation in patients with COVID-19 and shock.

Recommendation:

11. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest*** using buffered/balanced crystalloids over unbalanced crystalloids (weak recommendation, moderate quality evidence).

Rationale:

No direct evidence addresses this question in patients with COVID-19 and shock; the panel therefore based this recommendation on indirect evidence from critically ill patients in general.

A systematic review and meta-analysis of 21 RCTs (n = 20,213 patients) comparing intravenous buffered (balanced) crystalloid solutions versus 0.9% saline for resuscitation of critically ill adults and children (55) reported no significant differences in hospital mortality (OR, 0.91; 95% CI, 0.83 to 1.01) or acute kidney injury (OR, 0.92; 95% CI, 0.84 to 1.00) between the treatments. However, the point estimates for both outcomes suggest a potential for benefit from buffered crystalloid solutions. In the absence of apparent harm, and considering the roughly equivalent costs, we suggest using buffered crystalloid solutions over unbalanced crystalloid solutions for resuscitation of patients with COVID-19 and shock. In settings with limited availability of buffered solutions, 0.9% saline remains a reasonable alternative.

Recommendation:

12. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***recommend*** against using hydroxyethyl starches (strong recommendation, moderate quality evidence).

Rationale:

Given the absence of direct evidence on patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general.

A systematic review of 69 RCTs (n = 30,020 patients) compared the use of crystalloids versus colloids in critically ill patients; 24 of these RCTs (n = 11,177 patients) compared the use of crystalloids with the use of starches (54). When the data were pooled, no statistically significant difference in mortality was observed at the end of follow-up (RR, 0.97; 95% CI, 0.86 to 1.09), within 90 days (RR, 1.01; 95% CI, 0.90 to 1.14), or within 30 days (RR, 0.99; 95% CI, 0.90 to 1.09). The authors, however, reported an increased risk of blood transfusion (RR, 1.19; 95% CI, 1.02 to 1.39) and renal replacement therapy (RRT) with starches (RR, 1.30; 95% CI, 1.14 to 1.48). Given the risk of clinically significant harm and of the apparent absence of benefits from the use of hydroxyethyl starches, we recommend against their use for resuscitation of patients with COVID-19 and shock.

Recommendation:

13. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** using gelatins (weak recommendation, low-quality evidence).

Rationale:

Because no study has evaluated this question in patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general.

In a systematic review of 69 RCTs (n = 30,020 patients) comparing crystalloid versus colloid use in critically ill patients, crystalloids were compared with gelatins in 6 RCTs (n = 1,698) (54). No statistically significant difference in all-cause mortality was observed at the end of the follow-up (RR, 0.89; 95% CI, 0.74 to 1.08), within 90 days (RR, 0.89; 95% CI, 0.73 to 1.09), or within 30 days (RR, 0.92; 95% CI, 0.74 to 1.16), although point estimates favored the use of crystalloids. Considering the absence of any benefit of gelatins, and their higher costs, we suggest against using gelatins for resuscitation of patients with COVID-19 and shock.

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Recommendation:

14. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** using dextrans (weak recommendation, low-quality evidence)

Rationale:

Given the absence of direct evidence on patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general.

A systematic review and meta-analysis on crystalloid versus colloid use in critically ill patients identified 19 trials comparing crystalloids with dextrans (n = 4,736) (54). It reported similar mortality rates at the end of follow-up (RR, 0.99; 95% CI, 0.88 to 1.11) and within 90 days (RR, 0.99; 95% CI, 0.87 to 1.12), but a possibly increased risk of blood transfusion in the dextran arm (RR, 0.92; 95% CI, 0.77 to 1.10).

In view of a possible increased risk of blood transfusion (bleeding) and higher costs associated with dextrans, we suggest against their use for resuscitation of patients with COVID-19 and shock.

Recommendation*:*

15. For the **acute resuscitation** of adults with **COVID-19 and shock**, we ***suggest against*** the routine use of albumin for initial resuscitation (weak recommendation, moderate quality evidence).

Rationale:

Since there is no direct evidence on patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general.

A systematic review and meta-analysis identified 20 RCTs (n = 13,047) comparing albumin with crystalloid use (54). It demonstrated no significant difference in all-cause mortality at the end of the follow-up (RR, 0.98; 95% CI, 0.92 to 1.06), within 90 days (RR, 0.98; 95% CI, 0.92 to 1.04), or within 30-days (RR, 0.99; 95% CI, 0.93 to 1.06). The risks of blood transfusion (RR, 1.31; 95% CI, 0.95 to 1.80) and RRT (RR, 1.11; 95% CI, 0.96 to 1.27) were also similar.

In the absence of a benefit of albumin, and considering its cost and limited availability, we suggest against its routine use for the initial resuscitation of patients with COVID-19 and shock.

Vasoactive Agents

Recommendation:

16. For adults with **COVID-19 and shock**, we ***suggest*** using norepinephrine as the first-line vasoactive agent, over other agents (weak recommendation, low-quality evidence).

Rationale:

There is no direct evidence on patients with COVID-19 and shock, therefore the panel based this recommendation on indirect evidence from critically ill patients in general.

A systematic review of 28 RCTs (n = 3,497 patients) and a clinical practice guideline from 2016 summarized the available body of evidence on the best first-line vasopressor for patients with shock (56, 57).

As norepinephrine is the most widely studied vasoactive agent with a low a priori risk of undesirable effects, we suggest using norepinephrine as the first-line vasoactive agent in patients with COVID-19 and shock.

Recommendation:

17. If norepinephrine is not available, we ***suggest*** using either vasopressin or epinephrine as the first-line vasoactive agent, over other vasoactive agents, for adults with **COVID-19 and shock** (weak recommendation, low-quality evidence).

Rationale:

In the absence of direct evidence on patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general. In a systematic review of 28 RCTs (n = 3,497 patients) norepinephrine was compared with both vasopressin and epinephrine, but no trials directly compared the two options (57). If norepinephrine is not available, we suggest using either vasopressin or epinephrine, as both agents have been assessed in RCTs without showing clear evidence of harm. Factors determining the choice between vasopressin and epinephrine may include availability and contraindications to the two agents. With vasopressin, digital ischemia may be a concern; with epinephrine, tachycardia and excess lactate production may be considerations.

Recommendation:

18. For adults with **COVID-19 and shock**, we ***recommend against*** using dopamine if norepinephrine is available (strong recommendation, high quality evidence).

Rationale:

Because no direct evidence addresses this question in patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients.

A 2016 Cochrane systematic review found six RCTs (n = 1,400) comparing norepinephrine and dopamine in patients with shock (57). When pooled, the results showed no significant difference in all-cause mortality, but the point estimate favored norepinephrine (RR, 1.07; 95% CI, 0.99 to 1.16), and an increased risk of arrhythmias (RR, 2.34; 95% CI, 1.46 to 3.78) was found in the dopamine arm.

On the basis of an increased risk of harm, including a possible increased risk of mortality in patients treated with dopamine, we recommend against using dopamine in patients with COVID-19 and shock where norepinephrine or alternatives are available (see recommendation 17).

Recommendation:

19. For adults with **COVID-19 and shock**, we ***suggest*** adding vasopressin as a second-line agent, over titrating norepinephrine dose, if target mean arterial pressure (MAP) cannot be achieved by norepinephrine alone (weak recommendation, moderate quality evidence).

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Rationale:

In the absence of data on patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general.

In a recent clinical practice guideline, the use of vasopressin and vasopressin analogs in critically ill adults with distributive shock was assessed (58). Analyzing 25 RCTS (n = 3,737 patients), the authors found low certainty of a reduction in mortality (RR, 0.91; 95% CI, 0.85 to 0.99), high certainty of a reduction in atrial fibrillation (RR, 0.77; 95% CI, 0.67 to 0.88), and moderate certainty of an increased risk of digital ischemia (RR, 2.56; 95% CI, 1.24 to 5.25) with the addition of vasopressin or its analogs to catecholamines. Another recent systematic review reached similar conclusion (59). In view of these findings, we suggest adding vasopressin as a second-line agent, over titrating norepinephrine dose, if target MAP cannot be achieved by norepinephrine alone in patients with COVID-19 and shock.

Recommendation:

20. For adults with **COVID-19 and shock**, we ***suggest titrating*** vasoactive agents to target a MAP of 60–65 mm Hg, rather than higher MAP targets (weak recommendation, low-quality evidence)

Rationale:

No direct evidence informs this recommendation; it is based on indirect evidence from critically ill patients.

A recent individual patient-data meta-analysis of two RCTs (n = 894 patients) comparing higher versus lower blood pressure targets for vasopressor therapy in adult patients with shock reported no significant difference in 28-day mortality (OR, 1.15; 95% CI, 0.87 to 1.52), 90-day mortality (OR, 1.08; 95% CI, 0.84 to 1.44), myocardial injury (OR, 1.47; 95% CI, 0.64 to 3.56), or limb ischemia (OR, 0.92; 95% CI, 0.36 to 2.10) (60). The risk of arrhythmias was increased in patients allocated to the higher target group (OR, 2.50; 95% CI, 1.35 to 4.77). Correspondingly, the recently published 65 trial reports an absolute risk difference in mortality of 3% (RR, 0.93; 95% CI, 0.85-1.03) in favor of a MAP target of 60–65 mm Hg (lower target), as compared to a standard of care MAP target (higher target) (61).

With an indication of improved outcome with lower MAP targets (and no firm indication of harm), we suggest titrating vasoactive agents to a target of 60–65 mm Hg.

Recommendation:

21. For adults with **COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine**, we ***suggest*** adding dobutamine, over increasing norepinephrine dose (weak recommendation, very low-quality evidence).

Rationale:

In the absence of direct evidence in patients with COVID-19 and shock, the panel used indirect evidence from critically ill patients to inform this recommendation. In a clinical practice guideline from 2018 assessing the optimal inotropic agent in patients with acute circulatory failure (shock), no RCTs comparing dobutamine vs. placebo or no treatment were identified (62). Based on a physiological rationale, we suggest adding dobutamine, over no treatment, in patients with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and high doses of norepinephrine. The use of dobutamine in shock, including in COVID-19 patients with shock, is a research priority.

Recommendation:

22. For adults with **COVID-19 and refractory shock**, we ***suggest*** using low-dose corticosteroid therapy ("shock-reversal"), over no corticosteroid therapy (weak recommendation, low-quality evidence).

Remark: A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or intermittent doses.

Rationale:

Because no data exist on the use of steroids in patients with COVID-19 and shock, the panel based this recommendation on indirect evidence from critically ill patients in general. Both a 2018 systematic review of 22 RCTs (n = 7,297 patients) comparing low-dose corticosteroid therapy versus no corticosteroid therapy in adult patients with septic shock (63) and a clinical practice guideline (64) report no significant difference in short-term mortality (RR, 0.96; 95% CI, 0.91 to 1.02), long-term mortality (RR, 0.96; 95% CI, 0.90 to 1.02), or serious adverse events (RR, 0.98; 95% CI, 0.90 to 1.08). However, time to resolution of shock and length of stay in ICU and in hospital were shorter with corticosteroid therapy.

As time to resolution of shock and length of stay (especially in ICU) are important cost considerations, we suggest using low-dose corticosteroid therapy in patients with COVID-19 and refractory shock. Below, we provide further guidance on patients with COVID-19 and respiratory failure in the absence of refractory shock.

B) Ventilatory Support

The prevalence of hypoxic respiratory failure in patients with COVID-19 is 19% (12). Recent reports from China showed that 4% to 13% of COVID-19 patients in these studies received non-invasive positive pressure ventilation (NIPPV), and that 2.3% to 12% required invasive mechanical ventilation (**Table 3**) (1, 12, 42, 43, 65). Although the true incidence of hypoxic respiratory failure in patients with COVID-19 is not clear, it appears that about 14% will develop severe disease requiring oxygen therapy, and 5% will require ICU admission and mechanical ventilation (12). Another study reported on 52 critically ill COVID-19 patients; 67% of these patients had ARDS, 33 (63.5%) received high-flow nasal cannula (HFNC), 56% invasive mechanical ventilation, and 42% NIPPV (42).

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Risk Factors for Respiratory Failure. Risk factors associated with respiratory failure requiring mechanical ventilation are not clearly described in published reports, although from the limited available data, risk factors associated with a critical illness/ICU admission included older age (> 60 years), male gender, and the presence of underlying comorbidities such as diabetes, malignancy, and immunocompromised state (1, 12, 42, 43). The CDC reported an overall case-fatality rate (CFR) of 2.3%, with a CFR of 14.8% in patients aged 80 years or older. In critically ill patients, the CFR was 49.0%, and it was higher than 50% in those who received invasive mechanical ventilation. The presence of pre-existing comorbid conditions such as cardiovascular disease, diabetes, chronic respiratory disease, hypertension, and cancer were associated with higher risk of death (12).

Recommendations:

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).

Rationale:

A recent study described the disease course of 1,009 patients with COVID-19 in China and showed that 41% of all hospitalized patients and over 70% of those with severe disease required supplemental oxygen (1). In critically ill patients, hypoxia can be detrimental and is associated with poor outcomes (66). There are no randomized or non-randomized studies on the use of oxygen in adults with COVID-19. However, the panel used indirect evidence from the acutely ill population to inform the recommendations.

A systematic review and meta-analysis of 25 RCTs (16,037 patients) showed that a liberal oxygen strategy is associated with increased risk of hospital mortality (RR, 1.21; 95% CI, 1.03 to 1.43) in acutely ill patients (67). Furthermore, a meta-regression showed a linear association between risk of death and higher Spo_2 targets (67). The median Spo_2 in the liberal oxygen group was 96% (IQR, 96 to 98) across all trials. A recent clinical practice guideline recommended that Spo_2 be maintained no higher than 96% (68).

Subsequent trials provided further guidance on oxygenation targets. The ICU-ROX trial randomized 1000 critically ill patients to receive either conservative oxygen (based on a protocol to dial down oxygen) or usual care. This trial showed no difference in 180-day mortality between the two groups (OR, 1.05; 95% CI, 0.81 to 1.37) (69). The ICU-ROX trial did not compare hyperoxia with a conservative oxygen strategy; instead it compared usual care with a conservative oxygen strategy.

The recent LOCO2 trial randomized patients with ARDS to a conservative oxygen arm (target Spo_2 88% to 92%) or a liberal oxygen arm (target $Spo_2 \geq 96\%$). The trial was stopped early for futility and possible harm after 61 deaths had occurred in 205 included patients for 28-day mortality (risk difference [RD], 7.8%; 95% CI, −4.8 to 20.6) (70). At 90 days, the conservative oxygen arm had a higher risk of death (RD, 14.0%; 95% CI, 0.7 to 27.2).

Considering the associated patient harm at the extremes of Spo_2 targets and the increased cost of liberal oxygen use, as well as the potential to reduce equity if oxygen resources are depleted, the panel issued a strong recommendation against using oxygen to target $Spo_2 > 96\%$, and a strong recommendation to avoid lower values ($Spo_2 < 90\%$). Therefore, a reasonable Spo_2 range for patients receiving oxygen is 92% to 96%.

Recommendation:

25. For adults with COVID-19 and **acute hypoxemic respiratory failure** despite conventional oxygen therapy, we ***suggest using*** HFNC over conventional oxygen therapy (weak recommendation, low-quality evidence).

Rationale:

As there is no direct evidence on patients with COVID-19, the panel used indirect evidence from the critically ill population to inform this recommendation. In an RCT comparing HFNC with conventional oxygen therapy in patients with acute hypoxic respiratory failure, HFNC resulted in reduced 90-day mortality (OR, 0.42; 95% CI, 0.21 to 0.85), but did not reduce the risk of intubation (71). A systematic review and meta-analysis of nine RCTs (2,093 patients) showed that HFNC reduces intubation compared with conventional oxygen (RR, 0.85; 95% CI, 0.74 to 0.99), but does not affect the risk of death or ICU length of stay (72–74). Even though the evidence on mortality and length of stay was not as strong, the reduction in the need for intubation is an important finding, particularly from the perspective of pandemics such as COVID-19, where resources such as critical care beds and ventilators may become limited. In addition, in SARS, there are reports of increased transmission of disease to healthcare workers, especially nurses, during endotracheal intubation (OR, 6.6; 95% Cl, 2.3 to 18.9) (29, 75, 76). Although this is a finding based mostly on retrospective observational studies, HFNC does not seem to confer an increased risk of transmission of disease. In studies evaluating bacterial environmental contamination, HFNC presented a contamination risk similar to that of conventional oxygen (77). In SARS, healthcare workers exposed to HFNC were not at increased risk of developing disease (75). Finally, patients may find HFNC more comfortable than, or at least as comfortable as, conventional oxygen therapy (71, 74). Although some authors advised avoiding the use of HFNC in patients with COVID-19 due to the fear of disease transmission, studies supporting this advice are lacking (78). Although some have proposed that patients wear face masks while on HFNC therapy, we are uncertain about the efficacy and safety of this approach. This question could be addressed in future studies.

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Recommendation:

26. In adults with COVID-19 and **acute hypoxemic respiratory failure**, we ***suggest using*** HFNC over NIPPV (weak recommendation, low-quality evidence).

Rationale:

In adults with COVID-19 and acute respiratory failure, we suggest the use of HFNC over NIPPV. In an RCT comparing HFNC with NIPPV in patients with acute hypoxic respiratory failure, HFNC resulted in reduced mortality at 90 days (HR, 2.50; 95% CI, 1.31 to 4.78), but did not significantly affect the need for intubation (50% failure rate in NIPPV vs 47% in conventional oxygen and 40% in HFNC groups; $p = 0.18$) (71). Another meta-analysis comparing HFNC with NIPPV showed HFNC to decrease the need for intubation of patients, yet without significantly reducing mortality or ICU length of stay (72).

Additionally, patients may find HFNC more comfortable than NIPPV (71). Given the evidence for a decreased risk of intubation with HFNC compared with NIPPV in acute hypoxemic respiratory failure, and studies suggesting that NIPPV may carry a greater risk of nosocomial infection of healthcare providers, we suggest HFNC over NIPPV. However, any patients receiving HFNC or NIPPV should be monitored closely and cared for in a setting where intubation can be facilitated in the event of decompensation, as the failure rate may be high and emergency intubation in an uncontrolled setting may increase the risk of nosocomial infection of healthcare providers (79, 80).

Recommendations:

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 NIPPV with close monitoring and short-interval assessment for worsening of respiratory failure (weak recommendation, very 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).

Rationale:

In adults presenting with hypoxic respiratory failure from COVID-19, there is no direct evidence to support the use of NIPPV; furthermore, some prior studies suggested that it may be associated with an increased risk of infection transmission to healthcare workers. Meta-analyses of RCTs showed reductions in both intubation and mortality risks with NIPPV in hypoxic respiratory failure. However, these meta-analyses included studies focused on immunocompromised, acute cardiogenic pulmonary edema, or post-operative patients; their findings may therefore be less applicable to COVID-19 patients, in whom acute hypoxemic respiratory failure and ARDS are more common presentations. (43, 81–83) In acute hypoxemic respiratory failure with an etiology other than cardiogenic pulmonary edema, NIPPV has a high failure rate. In one RCT, failure was reported in 49% of patients with hypoxic respiratory failure ventilated with NIPPV; these patients therefore required intubation (71). In addition, patients with hypoxic respiratory failure randomized to NIPPV had higher mortality (28%; 95% CI, 21%–37%) than those treated with conventional oxygen therapy (23%; 95% CI, 16%-33%) or HFNC (13%; 95% CI, 7%–20%) ($p = 0.02$).

In a cohort of Middle East Respiratory Syndrome (MERS) patients, NIPPV was not associated with improved mortality or length of stay, compared with patients who were intubated without trying NIPPV (79). However, NIPPV was associated with a high failure rate (92.4%), leading to intubation. Patients who received NIPPV prior to intubation had increased inhaled nitric oxide requirements and increased mortality (79). Failure rates in other pandemics, such as influenza, H1N1 and SARS, range from 10% to 70%, while demonstrations of efficacy mainly come from case series and observational studies rather than RCTs, leading to practice variation. In China, the use of NIPPV for pandemic respiratory infection is common, whereas guidelines from Europe, Hong Kong, and the US advise against NIPPV as a first-line therapy in H1N1 (84). There are additional concerns over the use of NIPPV in respiratory pandemics like COVID-19: NIPPV may aggravate severe forms of lung injury as a result of injurious transpulmonary pressures and large tidal volumes (85, 86), and may delay initiation of invasive mechanical ventilation, leading to emergency or more unstable intubations that can increase the risk of transmission to the healthcare team (85). In addition, NIPPV is an aerosol-generating procedure that can increase the risk of transmission of disease to healthcare workers (29). Several other studies and meta-analyses of SARS have also highlighted the risk of nosocomial spread of the disease with NIPPV (76, 87).

The balance between benefit and harm when using NIPPV in adults with COVID-19 is unclear. If, in certain COVID-19 patients, other forms of respiratory failure, such as acute hypercapnic respiratory failure or acute cardiogenic pulmonary edema, are known to be the cause of respiratory failure, NIPPV may be beneficial (88, 89). However, because limited experience with NIPPV in pandemics suggests a high failure rate, we recommend that any patient receiving NIPPV be monitored closely and cared for in a setting where intubation can be facilitated in the event of decompensation (79, 80). However, when resources become stretched, there may be insufficient ability to provide invasive ventilation, and even a moderate chance of success with NIPPV may justify its use.

If NIPPV is used, helmet NIPPV is an attractive option, if available. A single-center RCT showed decreased intubation and improved mortality from NIPPV delivered by helmet in ARDS patients (90). Of particular importance in the setting of a pandemic such as COVID-19, NIPPV by helmet has also been shown to reduce exhaled air dispersion, whereas face masks were insufficient (91). However, helmet NIPPV is more expensive,

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and without direct evidence of benefit in COVID-19 patients, resources should not be utilized to acquire this equipment if is not already available. **Figure 2** summarizes the recommendations on HFNC and NIPPV in patients with COVID-19.

Invasive Mechanical Ventilation

Recommendation:

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).

Rationale:

Currently there are no studies addressing mechanical ventilation strategies in COVID-19 patients. However, the panel of experts believes that mechanically ventilated patients with COVID-19 should be managed similarly to other patients with acute respiratory failure in the ICU.

While mechanical ventilation is a potentially life-saving intervention, it can worsen lung injury and, through ventilator-induced lung injury (VILI), contribute to multiorgan failure in patients with ARDS (86). One of the main ventilator strategies to minimize VILI is low Vt ventilation.

A systematic review and meta-analysis of RCTs found an inverse association between larger Vt gradient and mortality (92). In addition, authors found that using a protocolized low Vt strategy with high PEEP (9 RCTs and 1,629 patients) reduced the risk of death (RR, 0.80; 95% CI, 0.66 to 0.98) (92). Our analysis of 5 RCTs (1181 patients) showed a reduction in hospital mortality with low Vt ventilation (RR, 0.73; 95% CI, 0.63 to 0.85) (93-98). On the basis of the available body of evidence, several guidelines recommended using low Vt (4–8 mL/kg of predicted body weight) in patients with ARDS (99, 100).

The panel judged the magnitude of benefit to be moderate, the cost to be low, and the intervention to be acceptable and feasible to implement, and they therefore issued a strong recommendation to use low Vt (4–8 mL/kg predicted body weight) when ventilating patients with ARDS (**Fig. 3**).

Practical Considerations:

The ARDSNet study protocol set the initial Vt at 6 mL/kg which can be increased to 8 mL/kg if the patient is double triggering or if inspiratory airway pressure decreases below PEEP (95).

Strict adherence to target Vt in spontaneously breathing patients with ARDS is a challenge; patient-ventilator dyssynchrony is not uncommon (101).

Recommendation:

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).

Rationale:

There are no clinical trials examining the effect of plateau pressure (Pplat) limitation on COVID-19 induced ARDS. However, there is a large body of indirect evidence in patients with ARDS. Along with low Vt ventilation, Pplat limitation is a lung protective strategy to limit VILI. A systematic review and meta-analysis of RCTs found that using a lung protective strategy including protocolized low Vt and Pplat < 30 cm H_2O (9 RCTs and 1,629 patients) reduced the risk of death (RR, 0.80; 95% CI, 0.66 to 0.98) (92). A subsequent meta-analysis of RCTs comparing ventilatory strategies with low and high Pplat in patients with ARDS (15 studies) found that short-term mortality was higher in patients with Pplat > 32 cm H_2O during the first week in the ICU (Day 1: RR, 0.77; 95% CI, 0.66 to 0.89;

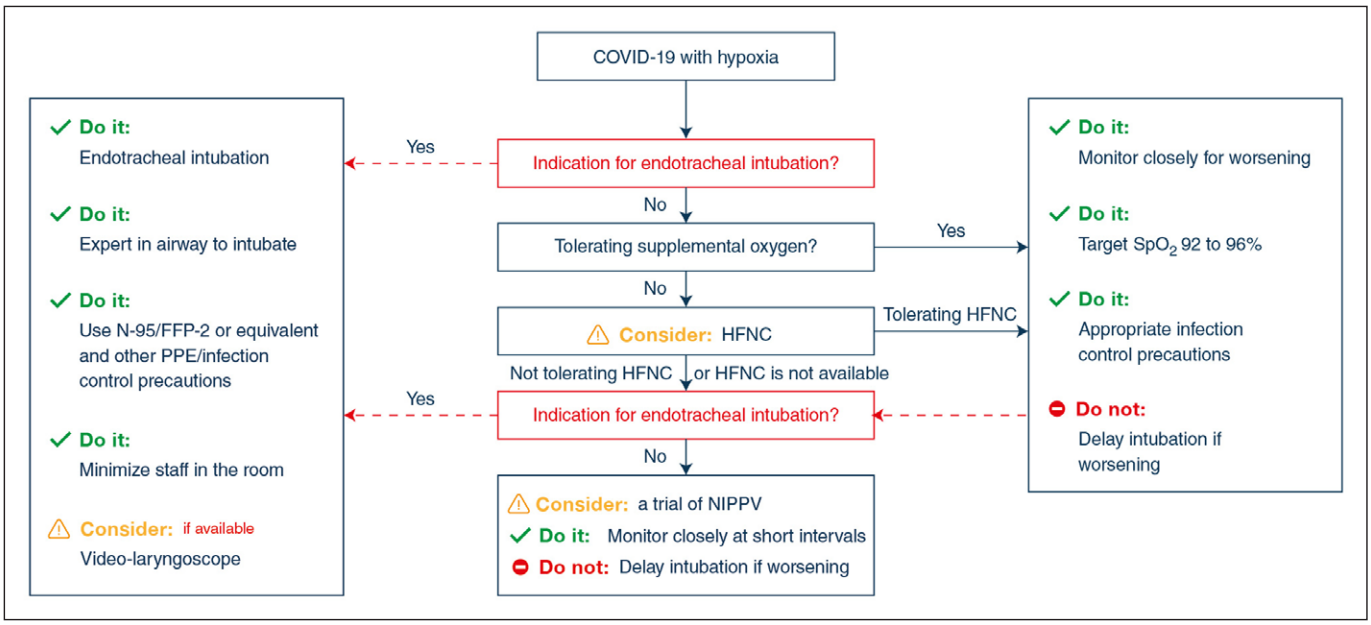

Figure 2. Summary of recommendations on the initial management of hypoxic COVID-19 patients.

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Day 3: RR, 0.76, 95% CI, 0.64 to 0.90; Day 7: RR, 0.78; 95% CI, 0.65 to 0.93)(102).

On the basis of the available body of evidence, several guidelines recommended keeping Pplat < 30 cm H_2O in patients with ARDS (99, 100). The panel judged the magnitude of benefit to be moderate, the cost to be low, the patients' values to be consistent, and the intervention to be acceptable and feasible to implement, and therefore, issued a strong recommendation to keep Pplat < 30 cm H_2O when ventilating patients with ARDS.

Practical Considerations:

The ARDSNet study protocol set the initial Vt at 6 mL/kg, and then measured Pplat (after a 0.5-second inspiratory pause) (95). If the Pplat > 30 cm H_2O, Vt could be reduced in 1 mL/kg (to 4 mL/kg) steps until Pplat was within range.

Recommendation:

32. For mechanically ventilated adults with COVID-19 and moderate to severe ARDS, we ***suggest*** using a higher PEEP strategy, over a lower PEEP strategy (weak recommendation, low-quality evidence).

Remark: If using a higher PEEP strategy (i.e., PEEP > 10 cm H_2O), clinicians should monitor patients for barotrauma.

Rationale:

In ARDS, extrinsic PEEP is used to prevent repeated opening and closing of alveoli (i.e. atelectotrauma), and therefore to reduce VILI. In addition, PEEP increases and sustains alveolar recruitment, which improves oxygenation and reduces oxygen requirement.

There are no clinical trials examining the effect of PEEP on coronavirus-induced ARDS. However, there is a large body of indirect evidence in patients with ARDS. An individual patient data meta-analysis (IPDMA) of the three largest trials (2,299 patients) of high PEEP (103–105) found no difference in in-hospital mortality in all patients (RR, 0.94; 95% CI, 0.86 to 1.04) (106). However, in patients with ARDS, a higher PEEP strategy resulted in lower ICU mortality (RR, 0.85; 95% CI, 0.76 to 0.95), lower in-hospital mortality (RR, 0.90; 95% CI, 0.81 to 1.0), and a reduction in the use of rescue therapies (RR, 0.63; 95% CI, 0.53 to 0.75), at the expense of a possible increase in the risk of pneumothorax (106).

A recent systematic review and meta-analysis of nine RCTs (3,612 patients) examined the effect of a higher PEEP strategy on patient-important outcomes (107). Overall, a higher PEEP strategy did not reduce hospital mortality (RR, 0.92; 95% CI, 0.79 to 1.07). However, in a subgroup of trials that enrolled patients with oxygenation response to PEEP (6 RCTS, 1,888 patients), the use of high PEEP significantly reduced in-hospital mortality, compared with a lower PEEP strategy (RR, 0.83; 95% CI, 0.69 to 0.98). Although the body of evidence suggests a beneficial effect of higher PEEP in selected patients, the results are likely to be confounded by the fact that low Vt ventilation was not used in the control arm of these trials (108).

There is no clear and agreed upon definition of higher PEEP; moreover, the optimal PEEP level in ARDS patients is unknown, and is likely to vary based on the extent of disease,

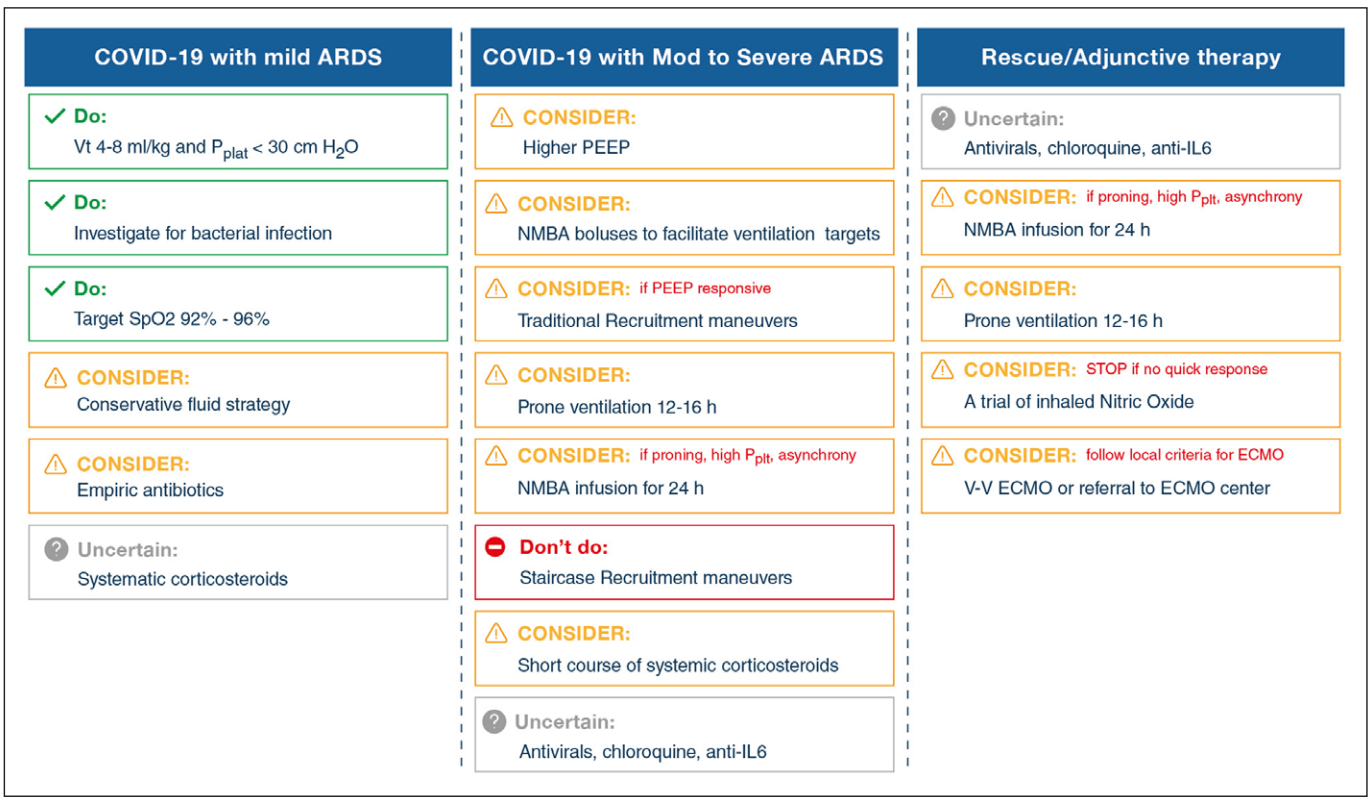

Figure 3. Summary of recommendations on the management of patients with COVID-19 and ARDS.

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lung compliance, and other factors. In the aforementioned IPDMA, the median PEEP level in the high PEEP arm was 15.3 and 13.3 cm H_2O on days 1 and 3, respectively, compared with median values of 9 and 8.2 cm H_2O on days 1 and 3 in the low PEEP arm (106). Although arbitrary, clinicians could consider PEEP levels > 10 cm H_2O to constitute a higher PEEP strategy, and PEEP levels < 10 cm H_2O as a lower PEEP strategy.

Practical Considerations:

Because the IPDMA combined different strategies to set higher PEEP, a reasonable starting point would be to implement a strategy used in the large RCTs that were included (i.e., ALVEOLI, LOV, and ExPRESS) (103–105). After increasing the PEEP level, clinicians should monitor their patients for evidence of barotrauma. Importantly, higher PEEP may result in higher Pplat, which is associated with its own risks and benefits when Pplat > 30 cm H_2O. Clinicians can use the ARDS Network protocol strategies to determine the optimal PEEP level. Other available strategies include decremental PEEP strategy, the esophageal balloon technique, and electrical impedance tomography. However, the effect of using these techniques on clinical outcomes is unknown.

Recommendation:

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).

Rationale:

The optimal fluid strategy in COVID-19 is not known, however, it is plausible that these patients will respond to fluid similarly to other ARDS patients. The limited data available on COVID-19 show that cardiac failure, alone or in combination with respiratory failure, was the cause of 40% of COVID-19 deaths (46). Another study showed that 44% of COVID-19 patients had arrhythmia (43). The data suggest the presence of myocardial injury in some patients with COVID-19. Few RCTs have been published that compare conservative or deresuscitative with liberal fluid strategies in ARDS. A recent systematic review included five RCTs enrolling 1,206 patients with ARDS. The risk of death was similar in both groups: 28% in the conservative fluid strategy group and 31.1% in the liberal strategy group (RR, 0.91; 95% CI, 0.77 to 1.07) (52). This study included RCTs in critically ill patients with or without ARDS, and the authors found that a conservative fluid strategy increased ventilator-free days (MD, 1.82 days; 95 % CI, 0.53 to 3.10 days) and reduced ICU length of stay (MD, −1.88 days; 95 % CI, −0.12 to −3.64 days), compared with a liberal fluid strategy. There was no difference in harm, including renal failure between the two groups. The landmark trial in ARDS patients (FACTT) found a significant reduction in the duration of mechanical ventilation with a conservative fluid strategy (109). Furthermore, the majority of patients with COVID-19 in the ICU are elderly, and may develop myocardial dysfunction that could limit their ability to handle large fluid volumes (46). In view of the moderate benefit observed in other ARDS populations, the possible reduced cost of administering less fluids, and the feasibility of the intervention, the panel issued a weak recommendation favoring conservative fluid strategy in patients with COVID-19 and ARDS.

Recommendation:

34. For mechanically ventilated adults with COVID-19 and **moderate to severe ARDS**, we ***suggest*** prone ventilation for **12 to 16 hours**, over no prone ventilation (weak recommendation, low-quality evidence).

Rationale:

In a series of 81 patients with COVID-19, radiographic features progressed over the first 1 to 2 weeks after symptom onset from predominant ground glass opacities to a mixed pattern of predominant basilar consolidation. This latter pattern may suggest a role for prone ventilation (110).

Prone positioning theoretically makes ventilation more homogeneous by decreasing ventral alveolar distention and dorsal alveolar collapse (111). This may reduce the difference between the dorsal and ventral transpulmonary pressures, in addition to reducing lung compression (112) and improving perfusion (113).

A recent study that described the clinical course of COVID-19 in the ICU showed that prone ventilation was used in 11.5% of patients (6 out of 52) (42). However, there are no studies available that describe the clinical course of patients with COVID-19 who were ventilated in the prone position.

A recent systematic review and meta-analysis of nine RCTs (2,129 patients) showed that prone ventilation for at least 12 hours in patients with moderate to severe ARDS reduced mortality (5 RCTs; RR, 0.74; 95% CI, 0.56 to 0.99), but had no effect on mortality in studies that used prone ventilation for < 12 hours (3 RCTs; RR, 1.03; 95% CI, 0.88 to 1.20). On the other hand, prone ventilation increased the risks of pressure sores (RR, 1.22; 95% CI, 1.06 to 1.41) and endotracheal tube obstruction (RR, 1.76; 95% CI, 1.24 to 2.50) (114). Other systematic reviews reached similar conclusions (115–117).

We have moderate certainty that prone ventilation for more than 12 hours in patients with moderate to severe ARDS reduces mortality, but may increase the risk of pressure sores and endotracheal tube obstruction. Healthcare workers proning patients with COVID-19 should be trained in the proper technique for proning and take infection control precautions in the event of accidental endotracheal tube disconnection from the ventilator. Proning itself is not associated with significant cost, and we believe that it may provide significant benefit. Further, proning can be implemented in low- and middle-income settings, and efforts should be made to provide the necessary training and education of healthcare workers to facilitate the practice (https://www.youtube.com/watch?v=E_6jT9R7WJs).

Practical Considerations:

A protocol for proning should be used at all institutions, based on the available resources and level of training. If prone

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ventilation is used, healthcare workers should be aware of complications such as pressure sores, vascular line and endotracheal tube displacement, facial edema, transient hemodynamic instability, corneal abrasions, brachial plexus injury, and hemodialysis vascular access flow issues.

In addition, clinicians should be familiar with the absolute contraindications for prone ventilation, such as unstable spine, open abdomen or open chest (i.e., surgery or trauma). Enteral nutrition via nasogastric or nasoduodenal tube can be continued during proning (118, 119).

Recommendations:

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

35.1. We ***suggest*** using, as needed, intermittent boluses of 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 hours (weak recommendation, low-quality evidence).

Rationale:

Several professional societies have issued recommendations on the use of NMBAs in ARDS (100, 120–123). Most issued recommendations favoring the use of an NMBA infusion in patients with moderate to severe ARDS. These recommendations were mostly based on the pooled estimates from three RCTs (431 patients) showing a reduction in 90-day mortality with an NMBA infusion as compared with no NMBA infusion (124). However, the results of the Re-evaluation of Systemic Early Neuromuscular Blockade (ROSE) trial challenged those of previous trials. The ROSE trial investigators randomized 1,006 patients with moderate or severe ARDS to receive either an infusion of NMBA for 48 hours or intermittent NMBA boluses on an as needed basis (125). The ROSE trial showed that a continuous infusion of cisatracurium did not improve any patient important outcomes.

Due to differences in design between the ROSE trial and the earlier trials, we did not perform a meta-analysis for mortality outcome, although the pooled estimate for barotrauma favored continuous NMBA infusion (RR, 0.55; 95% CI, 0.35 to 0.85). The panel suggests that a continuous NMBA infusion should be reserved for patients who have an indication for ongoing paralysis in which intermittent dosing may not suffice, such as patients with persistent ventilator dyssynchrony, and patients needing ongoing deep sedation prone ventilation, or persistently high plateau pressures. The effect of NMBAs on long-term outcomes is unclear.

Recommendations:

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 rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (weak recommendation, very low-quality evidence).

Rationale:

There are no studies that describe the use of pulmonary vasodilators in COVID-19 patients. A Cochrane review identified 13 RCTs (1,243 patients) on inhaled nitric oxide in ARDS; this treatment showed no significant effect on mortality (RR, 1.04; 95% CI, 0.9 to 1.19), and was associated with an increased risk of acute kidney injury (RR, 1.59; 95% CI, 1.17 to 2.16). Inhaled nitric oxide results in a transient improvement in oxygenation. The subgroup of studies reporting PaO_2/FiO_2 (mm Hg) values up to 24 hours after the intervention showed a statistically significant difference in favor of inhaled nitric oxide, which was not present beyond 24 hours. No study assessed the use of inhaled nitric oxide as a "rescue" therapy (126). Because of the possible harm from inhaled nitric oxide and the absence of a clear mortality benefit, the panel issued a strong recommendation against its routine use in patients with ARDS. However, in view of the finding of improved oxygenation, a trial of inhaled nitric oxide as a "rescue" therapy, after trying other options, is reasonable if available. If inhaled nitric oxide is used without a good response in terms of oxygenation, it should be tapered off to avoid rebound the pulmonary vasoconstriction that can occur with prolonged use and abrupt discontinuation.

No adequately powered RCTs have evaluated inhaled prostacyclins such as ilioprost, therefore, we could not recommend against or for their use in severe ARDS.

Recommendations:

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, moderate quality evidence).

Rationale:

No studies have assessed the role of recruitment maneuvers (RMs) in patients with ARDS secondary to COVID-19. RMs aim to improve oxygenation by increasing transpulmonary pressure to open atelectatic alveoli (127). However, exposure to high levels of positive pressure may lead to barotrauma, as well as cause transient hypotension in already critically ill and unstable patients.

We assessed eight indirect RCTs assessing RMs in ARDS patients, including patients with sepsis due to bacterial or viral pneumonia. Varying strategies were used to help recruit atelectatic lungs, however two strategies, in particular, were common

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in the 8 RCTs included in this meta-analysis. Traditional RMs are described as prolonged inspiratory holds for a set duration of time on higher levels of CPAP, most commonly 35 to 40 cm H_2O for 40 seconds (93, 104, 128, 129). Incremental PEEP titration RMs are described as incremental increases in PEEP from 25 to 35 to 45 cm H_20 for 1–2 minutes each (130–133). In a systematic review and meta-analysis of 6 RCTs (1,423 patients), RMs reduced mortality and the use of rescue interventions, and improved oxygenation at 24 hours without increasing the risk of barotrauma (134). Similarly, we identified eight RCTs (2,544 patients) that reported on in-hospital mortality. In these studies, RMs were not associated with reduced mortality (RR, 0.90; 95% CI, 0.78 to 1.04). However, subgroup analyses suggested that traditional RMs significantly reduced mortality (RR, 0.85; 95% CI, 0.75 to 0.97), whereas incremental PEEP titration RMs increased mortality (RR, 1.06; 95% CI, 0.97 to 1.17). While the effects of RMs on oxygenation may be transient, the studies showed a significant improvement in oxygenation after 24 hours. Trials used different PEEP strategies in intervention and control arms; RMs are best combined with a higher PEEP strategy.

Patients with severe ARDS and hypoxemia may benefit from traditional recruitment maneuvers along with higher levels of PEEP, but evidence specific to COVID-19 is needed. Patients receiving RMs should be monitored closely for severe desaturation, hypotension or barotrauma. RMS should be stopped if they lead to patient deterioration.

Recommendation:

40. In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we ***suggest*** using veno-venous (VV) 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.

Rationale:

There are no clinical trials of ECMO in COVID-19 patients. A recent report from China suggested that 11.5% of COVID-19 cases in the ICU received ECMO (42), but the clinical courses and the outcomes of these patients have not been reported yet.

The Ministry of Health in Saudi Arabia established an ECMO program during the MERS-CoV epidemic. In a retrospective cohort study of 35 patients with MERS-CoV and refractory hypoxemia, the group of patients who received VV ECMO had lower in-hospital mortality (65 vs 100%, $P = 0.02$) (135). However, this cohort study is at high risk of selection bias given its retrospective design.

Only two RCTs have evaluated ECMO vs. conventional mechanical ventilation in severe ARDS. Guidelines published in 2017 were unable to provide specific guidance on the use of ECMO, and further research was recommended (99). Although the most recent RCT (EOLIA) was stopped early for futility (136), a re-analysis of this trial using a Bayesian approach provided a more favorable interpretation, suggesting lower mortality with ECMO in severe ARDS (137). A recent systematic review including two RCTs (429 patients) found a reduction in 60-day mortality with ECMO (RR, 0.73; 95% CI, 0.58 to 0.92), but the risk of major bleeding was higher with ECMO (138).

ECMO is a resource-intensive technique restricted to specialized centers, and it remains an extremely limited resource. Therefore, its use as a rescue therapy should be reserved for carefully selected patients (139). Future studies describing the outcomes of COVID-19 patients on ECMO and the mechanisms of death will advance our understanding and guide practice.

IV. COVID-19 THERAPY

In this section we will discuss possible treatment options for SARS-CoV-2 and its complications, including antiviral agents, immunosuppressive agents, immunomodulators and other therapies.

Cytokine Storm Syndrome

Cytokine storm syndrome is a hyperinflammatory state that is characterized by fulminant multi-organ failure and elevation of cytokine levels. A recent study from China showed that COVID-19 is associated with a cytokine elevation profile that is reminiscent of secondary hemophagocytic lymphohistiocytosis (HLH) (44). Some authors even suggest that we screen critically ill COVID-19 patients for secondary HLH using the Hscore (140), and that corticosteroids and other immunosuppressive agents can be used in patients with a high likelihood of HLH (141). More evidence is needed before we can make recommendations on the treatment options for cytokine storm.

Recommendations:

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

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at 1–2 mg/kg/day for 5 to 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; 1,060 patients; RR, 0.45; 95% CI, 0.26 to 0.79), ARDS (4 RCTs; 945 patients; RR 0.24, 95% CI 0.10 to 0.56) and the duration of hospitalization (6 RCTs; 1,499 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 to 3.69), but the effect in the patients with other coronaviruses was unclear (OR, 0.83; 95% CI, 0.32 to 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 seven RCTs enrolling 851 patients with ARDS. The use of corticosteroids reduced mortality (RR, 0.75; 95% CI, 0.59 to 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 to 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 to 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 to 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.

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 deescalation 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 co-infection 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 *Staphylococcus 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

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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.

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 1,099 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 (1,785 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 to 1.31), ICU length of stay (MD, −0.07 days; 95% CI, −0.70 to 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 COVID-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.

Recommendation:

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

Recommendation:

46. In critically ill adults with COVID-19, we ***suggest against*** the routine use of convalescent plasma (Weak recommendation, very 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-CoV-2-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 to 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 MERS-CoV 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% CI, −17.3 to 5.7) or time to clinical improvement (MD, 1.31 days; 95% CI, 0.95 to 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 the 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 vitro* studies (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 the USA (clinicaltrials.gov NCT04280705). We will update our guidelines as new evidence emerges.

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 LLC-MK2 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 to 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

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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.

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 (207–209). 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 (210). 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 (211). 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 (212). 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 (213). 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 physiologically based pharmacokinetic models (209). 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 (209). A recent systematic review found no published studies in COVID-19 patients (214). Pending the results of ongoing trials, we were unable to issue a recommendation for or against chloroquine.

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 interleukin (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 (215-218). 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 (219). 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 six 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 to 1.86), and an increased risk of infections (OR, 1.30; 95% CI, 1.07 to 1.58) (220). 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 to 2.25) (221). Because 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 (222). However, in hospitalized patients with severe acute respiratory infection in Mexico, nitazoxanide was not found to be superior to placebo (223).

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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). Dr. Eddy Fan declared receiving consultancy fees from ALung Technologies and MC3 Cardiopulmonary. Dr. Maurizio Cecconi declared consultancy work with Edwards Lifesciences, Directed Systems, and Cheetah Medical. Dr. Lennie Derde is the NVIC (Dutch National ICU society) chair of Taskforce Infectious Diseases (standing committee), member of ESICM Coronavirus Taskforce (started with this outbreak), chair ESICM Clinical Training Committee, all are unpaid positions. Dr. Frederick Hyden is non-compensated consultant to Gilead Sciences (antivirals for RVIS including remdesivir), Regeneraon (monoclonals for RVIs including MERS), and SAB Biotherapeutics (polyclonal antibodies for RVIs including MERS). The remaining authors have disclosed that they have no potential conflicts of interest.

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