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ONLINE SPECIAL ARTICLE

Surviving Sepsis Campaign Guidelines on the Management of Adults With Coronavirus Disease 2019 (COVID-19) in the ICU: First Update

BACKGROUND: The coronavirus disease 2019 pandemic continues to affect millions worldwide. Given the rapidly growing evidence base, we implemented a living guideline model to provide guidance on the management of patients with severe or critical coronavirus disease 2019 in the ICU.

METHODS: The Surviving Sepsis Campaign Coronavirus Disease 2019 panel has expanded to include 43 experts from 14 countries; all panel members completed an electronic conflict-of-interest disclosure form. In this update, the panel addressed nine questions relevant to managing severe or critical coronavirus disease 2019 in the ICU. We used the World Health Organization's definition of severe and critical coronavirus disease 2019. The systematic reviews team searched the literature for relevant evidence, aiming to identify systematic reviews and clinical trials. When appropriate, we performed a random-effects meta-analysis to summarize treatment effects. We assessed the quality of the evidence using the Grading of Recommendations, Assessment, Development, and Evaluation approach, then used the evidence-to-decision framework to generate recommendations based on the balance between benefit and harm, resource and cost implications, equity, and feasibility.

RESULTS: The Surviving Sepsis Campaign Coronavirus Diease 2019 panel issued nine statements (three new and six updated) related to ICU patients with severe or critical coronavirus disease 2019. For severe or critical coronavirus disease 2019, the panel strongly recommends using systemic corticosteroids and venous thromboprophylaxis but strongly recommends against using hydroxychloroquine. In addition, the panel suggests using dexamethasone (compared with other corticosteroids) and suggests against using convalescent plasma and therapeutic anticoagulation outside clinical trials. The Surviving Sepsis Campaign Coronavirus Diease 2019 panel suggests using remdesivir in nonventilated patients with severe coronavirus disease 2019 and suggests against starting remdesivir in patients with critical coronavirus disease 2019 outside clinical trials. Because of insufficient evidence, the panel did not issue a recommendation on the use of awake prone positioning.

CONCLUSION: The Surviving Sepsis Campaign Coronavirus Diease 2019 panel issued several recommendations to guide healthcare professionals caring for adults with critical or severe coronavirus disease 2019 in the ICU. Based on a living guideline model the recommendations will be updated as new evidence becomes available.

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In response to the COVID-19 pandemic, the Surviving Sepsis Campaign (SSC) published recommendations on the management of critically ill coronavirus disease 2019 (COVID-19) patients (1, 2). In view of evolving

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evidence, the SSC COVID-19 panel convened to issue updated recommendations.

METHODS

We used the World Health Organization (WHO) definition of severe and critical COVID-19 (**Table 1**). We used similar methodology to the first iteration of the SSC COVID-19 guidelines, but we formally used the evidence to decision (EtD) framework to generate recommendations (3). More details about the methods can be found in the **Supplement** and **Figures S1-S3** (http://links.lww.com/CCM/G188). Detailed evidence profiles and evidence to decision tables are presented in **Tables S1-S23** (http://links.lww.com/CCM/G188). We present the updated guidelines' statements and recommendations in **Table 2** and the complete list of recommendations in **Table 3**.

I. MANAGEMENT OF RESPIRATORY FAILURE IN NONINTUBATED PATIENTS

Awake Prone Positioning

Statement:

1. There is insufficient evidence to issue a recommendation on the use of awake prone positioning in nonintubated adults with severe COVID-19.

Rationale: The concept of awake prone positioning derives from literature in mechanically ventilated patients, where prone ventilation improves secretion drainage, increases aeration to the atelectatic lung bases (4), alleviates the heart weight, and decompresses the left and right lower lobes (5). Furthermore, it homogenizes the transpulmonary pressure, reduces the lung strain (6), and reduces ventilation-perfusion mismatches (7). It is unclear whether similar effects occur in awake, nonsedated, nonventilated patients, and whether these effects impact patient-important outcomes.

Our updated search identified a systematic review that summarized the evidence on awake prone positioning, including 35 observational studies (n = 414 patients, 12 prospective cohorts, 18 retrospective cohorts, and 5 case reports) in ICU and non-ICU settings; 29 of these studies included COVID-19 patients (8). Prone positioning was protocolized in 15 studies, and the duration of the time spent in the prone position varied considerably among studies. All reports showed an improvement in oxygenation while in prone position; however, the magnitude of improvement was imprecise. Furthermore, improvements in oxygenation were lost once patients reverted to the supine position. Given the lack of randomization and control arms, the transient improvement in oxygenation, and uncertainty about the safety of this intervention and its effect on patient-important outcomes (e.g., endotracheal intubation and mortality), we were not able to issue a recommendation on the use of awake prone positioning. There are ongoing trials (ClinicalTrials.gov Identifiers: NCT04350723 NCT04407468, NCT04477655, NCT04395144, NCT04347941, NCT04547283, NCT04344587) that, when completed, will inform future recommendations. We do note that a benefit of prone position therapy is active patient engagement in self-care and is a metric that may not be captured in clinical trials focused on more usual outcome metrics such as duration of care, oxygenation, and in-hospital complications.

TABLE 1.
Definitions of Critical and Severe COVID-19

Category	Definition
Severe	Clinical signs of pneumonia (fever, cough, dyspnea, fast breathing) **and** one of the following: • Respiratory rate > 30 breaths/min; • Severe respiratory distress; or • Oxygen saturation < 90% on room air
Critical	Presence of acute respiratory distress syndrome or respiratory failure requiring ventilation, sepsis, or septic shock

II. COVID-19 PHARMACOTHERAPY

In this section we discuss potential therapeutic options for adults with severe or critical COVID-19 in the ICU including antiviral agents, immunosuppressive agents, anticoagulation, and immunomodulators.

Corticosteroids

Recommendations:

2. For adults with severe or critical COVID-19, we recommend using a short course of systemic corticosteroids over not using corticosteroids (strong recommendation, moderate-quality evidence).
3. For adults with severe or critical COVID-19 who are considered for systemic corticosteroids, we suggest using

TABLE 2.
Recommendations and Statements

Previous SSC COVID-19 Guideline	New SSC COVID-19 Guideline	
Recommendation/ Statement	Recommendation/Statement	Justification
Ventilation		
Not applicable	1. There is insufficient evidence to issue a recommendation on the use of awake prone positioning in nonintubated adults with severe COVID-19.	• Uncertainty about the balance between benefit and harm • Awaiting the results of ongoing RCTs
Therapy		
No recommendation	2. For adults with severe or critical COVID-19, we recommend against using hydroxychloroquine (strong recommendation).	• Moderate-quality evidence showed no effect on mortality or need for mechanical ventilation
In mechanically ventilated adults with COVID-19 and respiratory failure (without ARDS), we suggest against the routine use of systemic corticosteroids. In mechanically ventilated adults with COVID-19 and ARDS, we suggest using systemic corticosteroids over not using corticosteroids.	3. For adults with severe or critical COVID-19, we recommend using a short course of systemic corticosteroids over not using corticosteroids (strong recommendation).	• High-quality evidence showing reduction in death • Minimal adverse effects with short course of corticosteroids • Corticosteroids are affordable and widely available
Not applicable	4. For adults with severe or critical COVID-19 who are considered for systemic corticosteroids, we suggest using dexamethasone over other corticosteroids (weak recommendation). *Remark*: If dexamethasone is not available, clinicians may use other corticosteroids in doses equivalent to 6 mg daily of dexamethasone for up to 10 days.	• There are no trials comparing different corticosteroids with each other • Dexamethasone was associated with the largest treatment effect compared to no corticosteroids • Dexamethasone is widely available • It remains unclear whether this is a class effect or drug-specific effect
In critically ill adults with COVID-19, we suggest against the routine use of convalescent plasma.	5. For adults with severe or critical COVID-19, we suggest against the use convalescent plasma outside clinical trials (weak recommendation).	• Low-quality evidence from RCTs showed no improvement in outcomes • Awaiting the results of large ongoing RCT

(*Continued*)

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

Previous SSC COVID-19 Guideline	New SSC COVID-19 Guideline	
Recommendation/ Statement	Recommendation/Statement	Justification
No recommendation	6. For adults with severe COVID-19 who do not require mechanical ventilation, we suggest using IV remdesivir over not using it (weak recommendation). *Remark*: Remdesivir should *ideally* be started within 72 hours of positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction or antigen testing.	• The result of a placebo-controlled trial showed large reduction in time to recovery and hospital stay • Subgroup analysis from the three trials showed a discordant effect on mortality, suggesting a possible reduction in death in patients who are not invasively ventilated • Despite cost and limited availability, we believe that many patients, if presented with data, would prefer to receive remdesivir
No recommendation	7. For adults undergoing mechanical ventilation for critical COVID-19, we suggest against starting IV remdesivir (weak recommendation).	• Limited data on the effect of remdesivir on outcomes of mechanically ventilated patients • Until more data is available, current costs and limited drug availability favor a weak recommendation against its use in this population
Not applicable	8. For adults with severe or critical COVID-19, we recommend using pharmacologic VTE prophylaxis over not using prophylaxis (strong recommendation).	• High-quality indirect evidence from non-COVID-19 population shows that VTE prophylaxis is superior to no prophylaxis • VTE rates are higher in COVID-19 population
Not applicable	9. For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials (weak recommendation, very low quality evidence).	• Awaiting the publication of ongoing RCTs

ARDS = acute respiratory distress syndrome, COVID-19 = coronavirus disease 2019, RCT = randomized controlled trial, SSC = Surviving Sepsis Campaign, VTE = venous thromboembolism.

dexamethasone over other corticosteroids (weak recommendation, very low-quality evidence).

Remark: If dexamethasone is not available, clinicians may use other corticosteroids in doses equivalent to 6 mg daily of dexamethasone for up to 10 days.

Rationale: In the previous version of this guideline, the panel issued a weak recommendation for the use of corticosteroids in acute respiratory distress syndrome (ARDS) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), based on indirect evidence not specific to COVID-19 (1). Since then, multiple randomized controlled trials (RCTs) on the use of corticosteroids in COVID-19 patients have been published, including the RECOVERY trial (9, 10–12). These RCTs were summarized in a systematic review and meta-analysis that included a total of seven RCTs with

TABLE 3.
Updated List of SSC COVID-19 Recommendations

Recommendation	Strength
Infection Control and Testing	
For healthcare professionals performing aerosol-generating procedures on patients with COVID-19 in the ICU, we recommend using fitted respirator masks (N95 respirators, filtering facepiece 2, or equivalent) as opposed to surgical/medical masks, in addition to other PPE (e.g., gloves, gown, and eye protection, such as a face shield or safety goggles)	**Best practice statement**
We recommend performing aerosol-generating procedures on ICU patients with COVID-19 in a negative-pressure room.	**Best practice statement**
For healthcare professionals providing usual care for nonventilated COVID-19 patients, we suggest using surgical/medical masks as opposed to respirator masks, in addition to other PPE (e.g., gloves, gown, and eye protection, such as a face shield or safety goggles)	**Weak**
For healthcare professionals 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 PPE (e.g., gloves, gown, and eye protection, such as a face shield or safety goggles).	**Weak**
For healthcare professionals performing endotracheal intubation on patients with COVID-19, we suggest using video-guided laryngoscopy over direct laryngoscopy, if available.	**Weak**
For COVID-19 patients requiring endotracheal intubation, we recommend that endotracheal intubation be performed by the healthcare professional who is most experienced with airway management to minimize the number of attempts and risk of transmission.	**Best practice statement**
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**
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	
In adults with COVID-19 and shock, we suggest using dynamic parameters of skin temperature, capillary refill time, and/or serum lactate measurement over static parameters to assess fluid responsiveness.	**Weak**
For the acute resuscitation of adults with COVID-19 and shock, we suggest using a conservative over a liberal fluid strategy.	**Weak**
For the acute resuscitation of adults with COVID-19 and shock, we recommend using crystalloids over colloids.	**Weak**
For the acute resuscitation of adults with COVID-19 and shock, we suggest using buffered/balanced crystalloids over unbalanced crystalloids.	**Weak**
For the acute resuscitation of adults with COVID-19 and shock, we recommend against using hydroxyethyl starches.	**Strong**
For the acute resuscitation of adults with COVID-19 and shock, we suggest against using gelatins.	**Weak**

(*Continued*)

TABLE 3. (*Continued*).
Updated List of SSC COVID-19 Recommendations

Recommendation	Strength
For the acute resuscitation of adults with COVID-19 and shock, we suggest against using dextrans.	**Weak**
For the acute resuscitation of adults with COVID-19 and shock, we suggest against the routine use of albumin for initial resuscitation.	**Weak**
For adults with COVID-19 and shock, we suggest using norepinephrine as the first-line vasoactive agent over other agents.	**Weak**
For adults with COVID-19 and shock, if norepinephrine is not available, we suggest using either vasopressin or epinephrine as the first-line vasoactive agent over other vasoactive agents.	**Weak**
For adults with COVID-19 and shock, we recommend against using dopamine if norepinephrine is available.	**Strong**
For adults with COVID-19 and shock, we suggest adding vasopressin as a second-line agent over titrating norepinephrine dose, if target MAP cannot be achieved by norepinephrine alone.	**Weak**
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**
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**
Ventilation	
In adults with COVID-19, we suggest starting supplemental oxygen if the peripheral Spo_2 is < 92%, and recommend starting supplemental oxygen if Spo_2 is < 90%.	**Strong**
In adults with COVID-19 and acute hypoxemic respiratory failure on oxygen, we recommend that Spo_2 be maintained no higher than 96%.	**Strong**
For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, we suggest using HFNC over conventional oxygen therapy.	**Weak**
In adults with COVID-19 and acute hypoxemic respiratory failure, we suggest using HFNC over NIPPV.	**Weak**
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**
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**
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**
There is insufficient evidence to issue a recommendation on the use of awake prone positioning in nonintubated adults with severe COVID-19.	**No recommendation**
In mechanically ventilated adults with COVID-19 and ARDS, we recommend using low Vt ventilation (Vt 4-8 mL/kg of predicted body weight) over higher tidal volumes (Vt > 8 mL/kg).	**Strong**
For mechanically ventilated adults with COVID-19 and ARDS, we recommend targeting plateau pressure of < 30 cm H_2O.	**Strong**

(*Continued*)

TABLE 3. (*Continued*).
Updated List of SSC COVID-19 Recommendations

Recommendation	Strength
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**
For mechanically ventilated adults with COVID-19 and ARDS, we suggest using a conservative fluid strategy over a liberal fluid strategy.	**Weak**
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**
For mechanically ventilated adults with COVID-19 and moderate to severe ARDS: We suggest using as-needed intermittent boluses of NMBAs over continuous NMBA infusion to facilitate protective lung ventilation.	**Weak**
In the event of persistent ventilator dyssynchrony or 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**
In mechanically ventilated adults with COVID-19 ARDS, we recommend against the routine use of inhaled nitric oxide.	**Weak**
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**
For mechanically ventilated adults with COVID-19 and hypoxemia despite optimizing ventilation, we suggest using recruitment maneuvers over not using recruitment maneuvers.	**Weak**
If recruitment maneuvers are used, we recommend against using staircase (incremental PEEP) recruitment maneuvers.	**Strong**
In mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, we suggest using venovenous ECMO, if available, or referring the patient to an ECMO center. *Remark*: Because of the resource-intensive nature of ECMO and the need for experienced centers, healthcare professionals, and infrastructure, ECMO should be considered only for carefully selected patients with COVID-19 and severe ARDS.	**Weak**
Therapy	
For adults with severe or critical COVID-19, we recommend against using hydroxychloroquine.	**Strong**
For adults with severe or critical COVID-19, we recommend using a short course of systemic corticosteroids over not using corticosteroids.	**Strong**
For adults with severe or critical COVID-19 who are considered for systemic corticosteroids, we suggest using dexamethasone over other corticosteroids. *Remark*: If dexamethasone is not available, clinicians may use other corticosteroids in doses equivalent to 6 mg daily of dexamethasone for up to 10 days.	**Weak**

(*Continued*)

TABLE 3. (*Continued*).
Updated List of SSC COVID-19 Recommendations

Recommendation	Strength
For adults with severe COVID-19 who do not require mechanical ventilation, we suggest using IV remdesivir over not using it. *Remark*: Remdesivir should *ideally* be started within 72 hours of positive severe acute respiratory syndrome coronavirus 2 polymerase chain reaction or antigen testing.	**Weak**
For adults undergoing mechanical ventilation for critical COVID-19, we suggest against starting IV remdesivir.	**Weak**
For critically ill adults with COVID-19 who develop fever, we suggest using acetaminophen/paracetamol for temperature control over no treatment.	**Weak**
In critically ill adults with COVID-19, we suggest against the routine use of standard IV immunoglobulin.	**Weak**
For adults with severe or critical COVID-19, we suggest against the use convalescent plasma outside clinical trials.	**Weak**
For adults with severe or critical COVID-19, we recommend using pharmacologic VTE prophylaxis over not using prophylaxis.	**Strong**
For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials.	**Weak**

ARDS = acute respiratory distress syndrome, ECMO = extracorporeal membrane oxygenation, HFNC = high-flow nasal canula, MAP = mean arterial pressure, NIPPV = noninvasive positive pressure ventilation, NMBA = neuromuscular blocking agent, PEEP = positive end-expiratory pressure, PPE = personal protective equipment, Spo_2 = oxygen saturation, Vt = tidal volume, VTE = venous thromboembolism.

1,703 COVID-19 patients (13). Three trials used dexamethasone (14), three used hydrocortisone (11, 12), and one used methylprednisolone (15). Overall, the use of corticosteroids reduced the risk of 28-day mortality compared to no corticosteroids or placebo (OR 0.69; 95% CI 0.55 to 0.86; high quality). When only mechanically ventilated patients were included, the results were similar (OR 0.66; 95% CI 0.53 to 0.82; moderate quality). This translates to 96 fewer deaths (95% CI 142 fewer to 47 fewer) per 1,000 patients receiving corticosteroids (**Supplement**, http://links.lww.com/CCM/G188). The effect size for 28-day mortality was largest in the subgroup of trials using dexamethasone for up to 10 days (OR 0.64; 95% CI 0.50 to 0.82; moderate quality), followed by hydrocortisone (374 patients, OR 0.69; 95% CI 0.43 to 1.12, low quality) and methylprednisolone (47 patients, OR 0.97; 95% CI 0.77 to 1.22, very low quality). These differences in effect size could be related to between-study differences in sample size and design. Therefore, a firm conclusion on the comparative efficacy of different corticosteroids cannot be made. While most studies focused on early use of corticosteroids, the effect of late administration of corticosteroids in mechanically ventilated patients with COVID-19 remains unclear (16). Furthermore, the optimal dosing and duration of corticosteroid therapy is unclear. Until more evidence is available, we prefer using the dosing regimen from the RECOVERY trial (i.e., dexamethasone 6 mg/day for 10 days or equivalent).

Reporting of serious adverse events varied across trials. It is widely recognized that corticosteroids have a range of adverse effects. For viral pneumonia patients in the ICU, several studies have shown increased or prolonged coronaviral RNA shedding with corticosteroid use (10–12), potentially indicating active viral replication. However, the clinical consequences of increased viral shedding are uncertain, since the effects on duration of mechanical ventilation and hospital and ICU length of stay were not reported. Furthermore, indirect evidence from the non-COVID-19 ARDS population (7 RCTs, n = 851) suggests that corticosteroids reduce both

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) (17). Corticosteroids are widely available; dexamethasone is on the WHO's list of essential medicines. The cost implication for using a short course of corticosteroids is small and may result in cost savings, although formal cost-effectiveness studies are not available.

Considering the above rationale, the panel issued a strong recommendation for using a short course (up to 10 days) of corticosteroids in adults with severe or critical COIVID-19 and a suggestion to use dexamethasone over other corticosteroids.

ANTIVIRALS

Hydroxychloroquine

Recommendation:

4. For adults with severe or critical COVID-19, we recommend against using hydroxychloroquine (strong recommendation, moderate-quality evidence).

Rationale: In the first SSC COVID-19 guideline we were not able to issue a recommendation on the use of hydroxychloroquine because of a lack of data. Although in vitro studies suggest that chloroquine and hydroxychloroquine may inhibit SARS-CoV and SARS-CoV-2 replication (18–20), clinical trials have failed to demonstrate clinical benefit in hospitalized patients with COVID-19. Our updated search identified five new RCTs since the publication of the initial SSC COVID-19 guideline (21–25). Overall, the use of hydroxychloroquine in hospitalized adults with COVID-19 did not reduce 28-day mortality (RR 1.07; 95% CI 0.97 to 1.19; moderate quality) or the need for invasive ventilation (RR 1.11; 95% CI 0.90 to 1.36; moderate quality), but instead increased adverse events (RR 2.63; 95% CI 1.36 to 5.09; low quality) (Supplement, http://links.lww.com/CCM/G188). Similarly, an updated systematic review including both published and nonpublished data identified 26 RCTs with 10,012 patients and showed that the use of hydroxychloroquine was associated with a possible increase in risk of death (OR 1.11; 95% CI 1.02 to 1.20) (26). Subgroup analysis comparing hydroxychloroquine dosing (high versus low) found no subgroup effect.

The current body of evidence confirms that hydroxychloroquine does not reduce the risk of death in hospitalized patients with COVID-19, and may in fact cause harm. In addition, the routine use of hydroxychloroquine during this pandemic will likely increase costs and may reduce equity (Supplement, http://links.lww.com/CCM/G188). Considering this, the panel issued a strong recommendation against the use of hydroxychloroquine for the treatment of severe or critical COVID-19.

Convalescent Plasma

Recommendation:

5. For adults with severe or critical COVID-19, we suggest against the use of convalescent plasma outside clinical trials (weak recommendation, low-quality evidence).

Rationale: Researchers hypothesized that convalescent plasma (obtained from patients who had recovered from COVID-19) may provide passive immunity as a result of transfer of SARS-CoV-2-specific antibodies (27). Convalescent plasma has been used to treat several other viral infections, including those caused by SARS coronavirus, influenza A (H5N1) virus, and influenza A (H1N1) pdm09 virus (28–32). A meta-analysis of observational studies on passive immunotherapy for severe acute respiratory infections of viral etiology showed an association between convalescent plasma therapy and reductions in mortality (OR 0.25; 95% CI 0.14 to 0.45) (33). Despite the lack of a single RCT confirming its benefit, thousands of patients with COVID-19 have received convalescent plasma during this pandemic. We did not issue a recommendation in the previous version of this guideline because of the lack of data (1, 2). Since then, our search identified four new RCTs on the use of convalescent plasma in COVID-19 (34–37).

The largest RCT, the PLACID trial, enrolled 464 noncritical hospitalized adults with COVID-19 in 39 centers in India (34). Patients in the intervention group received two doses of 200 mL of convalescent plasma, 24 hours apart, while the control arm received usual care. Co-interventions (i.e., corticosteroids, hydroxychloroquine, and anticoagulation) were similar in both groups. At 28 days, there were no differences between the two groups in disease progression or mortality (RR 1.04; 95% CI 0.71 to 1.54) (34). Another RCT randomized 103 patients with severe and critical COVID-19 (25.8% were invasively ventilated) (35) to receive convalescent plasma or usual care. At 28 days, there was no significant difference between the two groups in

risk of death (OR 0.65; 95% CI 0.29 to 1.46). The findings of the other two trials were shared as preprints (36, 37). To summarize the evidence, we performed a meta-analysis of four RCTs (732 patients) and found that convalescent plasma did not reduce hospital mortality compared with usual care (RR 0.77; 95% CI 0.48 to 1.24; low quality). After we summarized the evidence, another trial was published, which randomized 228 patients with severe COVID-19 to receive either convalescent plasma or usual care. There were differences between the two groups in risks of death and other patient-important outcomes (38), which is consistent with the results of prior RCTs.

Although adverse events were not reported, the rate of adverse events from transfusing convalescent plasma (e.g., infusion reactions, volume overload, acute lung injury) appears to be low and similar to plasma transfusion in general (39). It should be noted that severity of illness has been associated with higher levels of antibody response (40), questioning the efficacy of convalescent plasma in patients with critical COVID-19 who may already have high antibody levels.

Convalescent plasma requires apheresis/plasmapheresis to collect samples from donors, which is costly and not widely available. In addition, the optimal neutralizing antibody titer for SARS-CoV-2 is unknown. It is likely that moderate-to-large amounts of resources are required to routinely implement convalescent plasma in a pandemic (Supplement, http://links.lww.com/CCM/G188). There are ongoing large trials that will provide higher-quality evidence on the efficacy and safety of convalescent plasma in patients with COVID-19. Considering the lack of benefit in published RCTs so far, low-quality evidence, uncertainty about some outcomes, associated costs, and feasibility issues, the panel issued a weak recommendation against using convalescent plasma in patients with severe or critical COVID-19 outside the context of clinical trials.

Remdesivir

Recommendations:

6. For adults with severe COVID-19 who do not require mechanical ventilation, we suggest using IV remdesivir over not using it (weak recommendation, moderate-quality evidence).

Remark: Remdesivir should *ideally* be started within 72 hours of positive SARS-CoV-2 polymerase chain reaction or antigen testing.

7. For adults undergoing mechanical ventilation for critical COVID-19, we suggest against starting IV remdesivir (weak recommendation, low-quality evidence).

Rationale: Remdesivir is the prodrug of an adenosine analogue, which incorporates into nascent viral RNA chains and results in premature chain termination. Remdesivir inhibits replication of coronaviruses in in vitro studies (41) and to a limited extent in a nonhuman primate model of SARS-CoV-2 (42). In the first SSC COVID-19 guideline we were not able to issue a recommendation on the use of remdesivir because of lack of data. Since then, four RCTs examining the efficacy and safety of remdesivir in COVID-19 have been published (25, 43–45). The ACTT-1 trial randomized 1,062 hospitalized adults with COVID-19 to receive either IV remdesivir (200 mg on day 1 followed by 100 mg daily for up to 9 days) or placebo for up to 10 days (43). Although 28-day mortality was lower in the remdesivir group, the 95% CI could not exclude no effect (HR 0.73; 95% CI 0.52 to 1.03). The primary outcome for this study was time to recovery, which was improved with the use of remdesivir (rate ratio 1.29; 95% CI 1.12 to 1.49), resulting in reduced hospital stay (MD −5.0 days; 95% CI −7.7 to −2.3) and need for invasive mechanical ventilation. However, subgroup analyses suggest that remdesivir reduced risk of death in patients receiving supplemental oxygen but not in those receiving high-flow nasal cannula (HFNC), invasive positive pressure ventilation (NIPPV), or invasive mechanical ventilation. Furthermore, remdesivir did not affect the duration of NIPPV or invasive mechanical ventilation.

More recently, the SOLIDARITY trial released its results as a preprint (25). In this trial, investigators randomized 11,266 hospitalized adults with COVID-19 to several arms, out of which 2,750 patients received remdesivir (similar dosing to the ACTT-1 trial) and 4,088 patients received no intervention. Remdesivir did not reduce the risk of death at 28 days (RR 0.95; 95% CI 0.81 to 1.11). The authors also conducted a meta-analysis that included all three trials with a total of 7,600 patients. Overall, the use of remdesivir did not reduce 28-day mortality (RR 0.91; 95%CI 0.79 to 1.05). However, a subgroup analysis by COVID-19 severity (ventilated vs nonventilated) showed that remdesivir may reduce death in hypoxemic patients on supplemental oxygen (RR 0.80; 95% CI 0.63 to 1.01, moderate quality) but not in the subgroup of ventilated patients (RR 1.16; 95% CI 0.85 to 1.60, low quality).

Our meta-analysis included the two placebo-controlled trials (41, 43) and suggested that remdesivir may reduce the time to clinical improvement (MD −3.8 days; 95% CI −5.7 to −1.9, moderate quality) in all hospitalized patients with COVID-19 and may reduce serious adverse events compared with usual care (Supplement, http://links.lww.com/CCM/G188). Only one trial (ACTT-1) was placebo controlled and reported on clinical recovery outcome. In this trial remdesivir shortened time to clinical recovery by 4 days (95% CI −7.15 to −0.85, low quality).

These findings suggest that patients with critical COVID-19 are less likely to benefit from remdesivir and that its use should be reserved for hospitalized patients with severe disease and those not receiving mechanical ventilation. In addition, the ACTT-1 trial randomized patients within 72 hours of positive testing for SARS-CoV-2; therefore, it is plausible to encourage initiating treatment as early as possible (within 72 hours of a positive SARS-CoV-2 test) for patients with severe COVID-19 in the ICU.

Recently, the WHO issued a weak recommendation against the use of remdesivir in hospitalized patients with COVID-19 regardless of disease severity (46). This recommendation seems to prioritize resources and equity rather than the discordant effect of remdesivir by disease severity. However, it remains a weak recommendation, which means that some patients and clinicians may still favor a therapeutic approach that includes remdesivir.

Considering the moderate-quality evidence of no mortality benefit, the uncertainty about the effect on other patient-important outcomes, associated costs, and feasibility issues (not widely available, IV formulation only), the panel issued a weak recommendation against starting remdesivir in mechanically ventilated patients with COVID-19 (Supplement, http://links.lww.com/CCM/G188). However, because of the possible effect of reducing mortality and duration of illness combined with fewer adverse events, the panel issued a weak recommendation favoring the use of remdesivir in severe COVID-19.

Anticoagulation

Recommendations:

8. For adults with severe or critical COVID-19, we recommend using pharmacologic venous thromboembolism (VTE) prophylaxis over not using prophylaxis (strong recommendation, moderate-quality evidence).
9. For adults with severe or critical COVID-19 and no evidence of VTE, we suggest against the routine use of therapeutic anticoagulation outside of clinical trials (weak recommendation, very low quality evidence).

Rationale: While pulmonary histopathologic findings in severe COVID-19 may be similar to viral ARDS, recent studies described some unique findings. Several case series showed evidence of severe endothelial injury and microvascular thrombosis (alveolar capillary microthrombi) (47–49). Clinical studies report high rates of VTE in hospitalized adults with COVID-19. A systematic review and meta-analysis of observational studies found a pooled prevalence of VTE of 26% (95% CI 20 to 32%) in hospitalized patients with COVID-19 (50).

Although no RCTs evaluated the efficacy of VTE pharmacologic prophylaxis in the COVID-19 population, evidence from the critically ill patient population may be applicable. A systematic review and meta-analysis of four RCTs that compared pharmacologic prophylaxis to no prophylaxis in critically ill patients found that pharmacologic prophylaxis, compared with no prophylaxis, reduces the risks of deep venous thrombosis (RR 0.51; 95% CI 0.41 to 0.63; moderate quality) and pulmonary embolism (RR 0.52; 95% CI 0.28 to 0.97, moderate quality), without increasing the risk of major bleeding (RR 0.82; 95% CI 0.56 to 1.21; moderate quality) (51). Several international guidelines recommend using pharmacologic VTE prophylaxis in critically ill patients (52). The panel considered the evidence to be applicable to COVID-19 patients and that this approach would be feasible and acceptable and would probably result in cost savings (Supplement, http://links.lww.com/CCM/G188). Therefore, we issued a strong recommendation for using pharmacologic VTE prophylaxis. Clinical trials demonstrate some benefit of low-molecular-weight heparin (LMWH) over unfractionated heparin (UFH) for VTE prevention in the critically ill population. A meta-analysis of three RCTs (n = 5188) found that LMWH probably reduces VTE without increasing the risk of bleeding (51). Another systematic review and meta-analysis of eight RCTs (including RCTs on trauma population) found that LMWH reduces VTE risk without increasing major bleeding compared to UFH (53). Therefore,

LMWH is preferred over UFH for VTE prophylaxis whenever available. Some clinicians advocate for using intermediate-dosing LMWH or UFH for adults with severe or critical COVID-19; however, there are no published RCTs comparing conventional dosing to intermediate-dosing prophylaxis.

It remains unclear whether therapeutic anticoagulation should be administered to COVID-19 patients without VTE. Despite the high prevalence of micro- and macrovascular thrombosis, no rigorous RCTs have examined the efficacy and safety of therapeutic anticoagulation in this population. D-dimer concentration has been proposed as a threshold trigger to provide therapeutic anticoagulation in some studies and local practices, but no robust data support this practice. A pilot RCT randomized 20 hospitalized mechanically ventilated patients with COVID-19 and elevated D-dimer level to receive either full-dose anticoagulation with enoxaparin or prophylactic-dose UFH or enoxaparin; however, this trial was underpowered to detect meaningful clinical differences (54). While several observational studies have suggested a benefit from therapeutic anticoagulation, these studies are at high risk of bias and should be considered only as hypothesis-generating (55–57).

Additionally, it is unclear which variables could increase the likelihood of VTE diagnosis during an ICU stay. A cohort study from the United States included 3,334 hospitalized COVID-19 patients, out of which 829 were admitted to the ICU (58). In this study, male sex and elevated D-dimer were the only variables significantly associated with VTE. In addition, higher D-dimer levels had stronger associations with VTE. For instance, a D-dimer level greater than 10,000 ng/mL was associated with an HR of 32 (95% CI 17.2 to 61.9) for VTE. Although D-dimer levels were elevated in patients with and without VTE, the median level was higher in patients with pulmonary embolism (1,748 ng/mL; IQR 398 to 10,000) compared with those without VTE (414 ng/mL; IQR 268 to 768). Nevertheless, there are different assays for measuring D-dimer levels with different diagnostic utility. While it is reasonable for clinicians to assess for VTE in COVID-19 patients with high or rapidly increasing D-dimer levels, a decision process based on D-dimer levels needs to be better studied before clinicians adopt an approach of empiric anticoagulation on this basis, especially since an elevated D-dimer level could also indicate bleeding (59), making clinical evaluation crucial before making decisions based on laboratory values.

Considering the uncertainty surrounding the efficacy and safety of using therapeutic anticoagulation in the absence of VTE, the panel issued a weak recommendation against the use of therapeutic anticoagulation outside clinical trials.

SUMMARY

In this evidence-based update of the SSC COVID-19 guidelines, the panel issued nine statements related to ICU patients with severe or critical COVID-19. For severe or critical COVID-19 the panel strongly recommends using systemic corticosteroids and venous thromboprophylaxis, and strongly recommends against using hydroxychloroquine. In addition, the panel suggests using dexamethasone (compared with other corticosteroids) and suggests against using convalescent plasma outside clinical trials. The SSC COVID-19 panel suggests using remdesivir in nonventilated patients with severe COVID-19 and suggests against starting remdesivir in patients with critical COVID-19 outside clinical trials. Because of insufficient evidence, the panel was not able to issue recommendations on the use of awake prone positioning or empiric therapeutic anticoagulation.

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