

5: Care of Critically Ill Patients With COVID-19

Last Updated: December 17, 2020

Summary Recommendations

Infection Control

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using an N95 respirator (or equivalent or higher-level respirator) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room, when available **(AIII)**.
- For health care workers who are providing usual care for nonventilated patients with COVID-19, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AII)**.
- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly **(BIII)**.
- The Panel recommends that endotracheal intubation in patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible **(AIII)**.
- The Panel recommends that intubation be performed using video laryngoscopy, if possible **(CIII)**.

Hemodynamics

- For adults with COVID-19 and shock, the Panel recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness **(BII)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids **(BII)**.
- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation **(BI)**.
- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock **(AI)**.
- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**. The Panel recommends adding either vasopressin (up to 0.03 units/min) **(BII)** or epinephrine **(CII)** to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/min) **(CII)** to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock **(AI)**.
- The Panel **recommends against** using low-dose dopamine for renal protection **(BII)**.
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents **(BII)**.
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available **(BIII)**.
- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy **(BII)**.

Oxygenation and Ventilation

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) **(BI)**.
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available **(BIII)**.
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to

improve oxygenation (**CIII**).

- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (**AIII**).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 exposure to health care practitioners during intubation (**AII**).
- For mechanically ventilated adults with COVID-19 and acute respiratory distress syndrome (ARDS):
 - The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AI**).
 - The Panel recommends targeting plateau pressures of <30 cm H₂O (**AII**).
 - The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BII**).
 - The Panel **recommends against** the routine use of inhaled nitric oxide (**AI**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BII**).
 - For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BII**).
- For mechanically ventilated adults with COVID-19 and moderate-to-severe ARDS:
 - The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIII**).
 - In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).
- For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:
 - The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CII**).
 - If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AII**).
 - The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (**CIII**).

Acute Kidney Injury and Renal Replacement Therapy

- For critically ill patients with COVID-19 who have acute kidney injury and who develop indications for renal replacement therapy, the Panel recommends continuous renal replacement therapy (CRRT), if available (**BIII**).
- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy rather than intermittent hemodialysis (**BIII**).

Pharmacologic Interventions

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (**AIII**).

Extracorporeal Membrane Oxygenation

- There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation in patients with COVID-19 and refractory hypoxemia.

Rating of Recommendations: A = Strong; B = Moderate; C = Optional

Rating of Evidence: I = One or more randomized trials with clinical outcomes and/or validated laboratory endpoints; II = One or more well-designed, nonrandomized trials or observational cohort studies; III = Expert opinion

General Considerations

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Severe cases of COVID-19 may be associated with hypoxemic respiratory failure, acute respiratory distress syndrome, septic shock, cardiac dysfunction, elevation in multiple inflammatory cytokines, thromboembolic disease, and/or exacerbation of underlying comorbidities. In addition to pulmonary disease, patients with COVID-19 may also experience cardiac, hepatic, renal, and central nervous system disease. Because patients with critical illness are likely to undergo aerosol-generating procedures, they should be placed in airborne infection isolation rooms, when available.

Guidance on diagnostic testing for severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) can be found in the [Testing for SARS-CoV-2 Infection](#) section.

Most of the recommendations for the management of critically ill patients with COVID-19 are extrapolated from experience with other causes of sepsis.¹ Currently, there is limited information to suggest that the critical care management of patients with COVID-19 should differ substantially from the management of other critically ill patients; however, taking special precautions to prevent environmental contamination by SARS-CoV-2 is warranted.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 includes treating both the medical condition that initially resulted in ICU admission and other comorbidities and nosocomial complications.

Comorbid Conditions

Certain attributes and comorbidities (e.g., older age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancer, renal disease, obesity, sickle cell disease, receipt of a solid organ transplant) are associated with an increased risk of severe illness from COVID-19.²

Bacterial Superinfection of COVID-19-Associated Pneumonia

Limited information exists about the frequency and microbiology of pulmonary coinfections and superinfections in patients with COVID-19, such as hospital-acquired pneumonia (HAP) and ventilator-associated pneumonia (VAP). Some studies from China emphasize the lack of bacterial coinfections in patients with COVID-19, while other studies suggest that these patients experience frequent bacterial complications.³⁻⁸ There is appropriate concern about performing pulmonary diagnostic procedures such as bronchoscopy or other airway sampling procedures that require disruption of a closed airway circuit. Thus, while some clinicians do not routinely start empiric broad-spectrum antimicrobial therapy for patients with severe COVID-19 disease, other experienced clinicians routinely use such therapy. However, empiric broad-spectrum antimicrobial therapy is the standard of care for the treatment of shock. Antibiotic stewardship is critical to avoid reflexive or continued courses of antibiotics.

Septic Shock and the Inflammatory Response Due to COVID-19

Patients with COVID-19 may express high levels of an array of inflammatory cytokines, often in the setting of deteriorating hemodynamic or respiratory status. This is often referred to as “cytokine release syndrome” or “cytokine storm,” although these are imprecise terms. Intensivists need to consider the full differential diagnosis of shock to exclude other treatable causes of shock (e.g., bacterial sepsis due to pulmonary or extrapulmonary sources, hypovolemic shock due to a gastrointestinal hemorrhage that is unrelated to COVID-19, cardiac dysfunction related to COVID-19 or comorbid atherosclerotic disease, stress-related adrenal insufficiency).

COVID-19-Induced Cardiac Dysfunction, Including Myocarditis

A growing body of literature describes cardiac injury or dysfunction in approximately 20% of patients who are hospitalized with COVID-19.^{4,6,9-12} COVID-19 may be associated with an array of cardiovascular complications, including acute coronary syndrome, myocarditis, arrhythmias, and thromboembolic disease.¹³

Thromboembolic Events and COVID-19

Critically ill patients with COVID-19 have been observed to have a prothrombotic state, which is characterized by the elevation of certain biomarkers, and there is an apparent increase in the incidence of venous thromboembolic disease in this population. In some studies, thromboemboli have been diagnosed in patients who received chemical prophylaxis with heparinoids.¹⁴⁻¹⁶ Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.¹⁷ Some authors have called for routine surveillance of ICU patients for venous thromboembolism.¹⁸ See the [Antithrombotic Therapy in Patients with COVID-19](#) section for a more detailed discussion.

Renal and Hepatic Dysfunction Due to COVID-19

Although SARS-CoV-2 is primarily a pulmonary pathogen, renal and hepatic dysfunction are consistently described in patients with severe COVID-19.⁴ In one case series, continuous renal replacement therapy was needed in more than 15% of cases of critical disease.⁶ See the [Acute Kidney Injury and Renal Replacement Therapy](#) section for a more detailed discussion.

Considerations in Children

Several large epidemiologic studies suggest that rates of ICU admission are substantially lower for children with COVID-19 than for adults with the disease. However, severe disease does occur in children.¹⁹⁻²⁴ The risk factors for severe COVID-19 in children have not yet been established. Data from studies of adults and extrapolation from data on other pediatric respiratory viruses suggest that children who are severely immunocompromised and those with underlying cardiopulmonary disease may be at higher risk for severe disease.

A new syndrome, multisystem inflammatory syndrome in children (MIS-C), which appears to be a postinfectious complication, has been described.^{25,26} Certain symptoms of MIS-C often require ICU-level care, including blood pressure and inotropic support. These symptoms include severe abdominal pain, multisystem inflammation, shock, cardiac dysfunction, and, rarely, coronary artery aneurysm. A minority of children with MIS-C meet the criteria for typical or atypical Kawasaki disease. For details on MIS-C clinical features and the treatments that are being investigated, see the [Special Considerations in Children](#) section.

Interactions Between Drugs Used to Treat COVID-19 and Drugs Used to Treat Comorbidities

All ICU patients should be routinely monitored for drug-drug interactions. The potential for drug-drug interactions between investigational medications or medications used off-label to treat COVID-19 and concurrent drugs should be considered.

Sedation Management in Patients with COVID-19

International guidelines provide recommendations on the prevention, detection, and treatment of pain, sedation, and delirium.^{27,28} Sedation management strategies, such as maintaining a light level of sedation (when appropriate) and minimizing sedative exposure, have shortened the duration of mechanical

ventilation and the length of stay in the ICU for patients without COVID-19.^{29,30}

The Society of Critical Care Medicine's (SCCM's) ICU Liberation Campaign promotes the ICU Liberation Bundle (A-F) to improve post-ICU patient outcomes. The A-F Bundle includes the following elements:

- A. Assess, prevent, and manage pain;
- B. Both spontaneous awakening and breathing trials;
- C. Choice of analgesia and sedation;
- D. Delirium: assess, prevent, and manage;
- E. Early mobility and exercise; *and*
- F. Family engagement and empowerment.

The A-F Bundle also provides frontline staff with practical application strategies for each element.³¹ The A-F Bundle should be incorporated using an interprofessional team model. This approach helps standardize communication among team members, improves survival, and reduces long-term cognitive dysfunction of patients.³² Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, the use of the Bundle should be encouraged, when appropriate, to improve ICU patient outcomes. Prolonged mechanical ventilation of COVID-19 patients, coupled with deep sedation and potentially neuromuscular blockade, increases the workload of ICU staff. Additionally, significant drug shortages may force clinicians to use older sedatives with prolonged durations of action and active metabolites, impeding routine implementation of the [PADIS Guidelines](#). This puts patients at additional risk for ICU and post-ICU complications.

Post-Intensive Care Syndrome

Patients with COVID-19 are reported to experience prolonged delirium and/or encephalopathy associated with mechanical ventilation.³³ Neurological complications are associated with older age and underlying conditions such as hypertension and diabetes mellitus.³⁴ Autopsy studies have reported both macrovascular and microvascular thrombosis, with evidence of hypoxic ischemia.³⁵ Adequate management requires careful attention to best sedation practices and vigilance in stroke detection.

Post-intensive care syndrome (PICS) is a spectrum of cognitive, psychiatric, and/or physical disability that affects survivors of critical illness and persists after a patient leaves the ICU.³⁶ Patients with PICS may present with varying levels of impairment; including profound muscle weakness (ICU-acquired weakness); problems with thinking and judgment (cognitive dysfunction); and mental health problems, such as problems sleeping, post-traumatic stress disorder (PTSD), depression, and anxiety. ICU-acquired weakness affects 33% of all patients who receive mechanical ventilation, 50% of patients with sepsis, and $\leq 50\%$ of patients who remain in the ICU for ≥ 1 week.³⁷⁻³⁹ Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.⁴⁰⁻⁴² About 50% of ICU survivors do not return to work within 1 year after discharge.⁴³ Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (using the A-F Bundle), physical rehabilitation, follow-up clinics, family support, and improved education about the syndrome. PICS also affects family members who participate in the care of their loved ones. In one study, a third of family members who had main decision-making roles experienced mental health problems such as depression, anxiety, and PTSD.⁴⁴

Early reports suggest that some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.⁴⁵ Although specific therapies for COVID-19-induced PICS are not yet available, physicians should maintain a high index of suspicion for cognitive impairment and other related

problems in survivors of severe or critical COVID-19 illness.

Other Intensive Care Unit-Related Complications

Patients who are critically ill with COVID-19 are at risk for nosocomial infections and other complications of critical illness care, such as VAP, HAP, catheter-related bloodstream infections, and venous thromboembolism. When treating patients with COVID-19, clinicians also need to minimize the risk of conventional ICU complications to optimize the likelihood of a successful ICU outcome.

Advance Care Planning and Goals of Care

The advance care plans and the goals of care for all critically ill patients must be assessed at hospital admission and regularly thereafter. This is an essential element of care for all patients. Information on palliative care for patients with COVID-19 can be found at the [National Coalition for Hospice and Palliative Care website](#).

To guide shared decision-making in cases of serious illness, advance care planning should include identifying existing advance directives that outline a patient's preferences and values. Values and care preferences should be discussed, documented, and revisited regularly for patients with or without prior directives. Specialty palliative care teams can facilitate communication between clinicians and surrogate decision makers, support frontline clinicians, and provide direct patient care services when needed.

Surrogate decision makers should be identified for all critically ill patients with COVID-19 at hospital admission. Infection-control policies for COVID-19 often create communication barriers for surrogate decision makers, and most surrogates will not be physically present when discussing treatment options with clinicians. Many decision-making discussions will occur via telecommunication.

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Infection Control

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Health care workers should follow the infection control policies and procedures issued by their health care institutions.

Recommendation

- For health care workers who are performing aerosol-generating procedures on patients with COVID-19, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using an N95 respirator (or equivalent or higher-level respirator) rather than surgical masks, in addition to other personal protective equipment (PPE) (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- Aerosol-generating procedures include endotracheal intubation and extubation, sputum induction, bronchoscopy, mini-bronchoalveolar lavage, open suctioning of airways, manual ventilation, unintentional or intentional ventilator disconnections, noninvasive positive pressure ventilation (NIPPV) (e.g., bilevel positive airway pressure [BiPAP], continuous positive airway pressure [CPAP]), cardiopulmonary resuscitation, and, potentially, nebulizer administration and high-flow oxygen delivery. Caution regarding aerosol generation is appropriate in situations such as tracheostomy and proning, where ventilator disconnections are likely to occur.

Rationale

During the severe acute respiratory syndrome (SARS) epidemic, aerosol-generating procedures increased the risk of infection among health care workers.^{1,2} N95 respirators block 95% to 99% of aerosol particles; however, medical staff must be fit-tested for the type used.³ Surgical masks block large particles, droplets, and sprays, but are less effective in blocking small particles (<5 µm) and aerosols.⁴

Recommendation

- The Panel recommends minimizing the use of aerosol-generating procedures on intensive care unit patients with COVID-19 and carrying out any necessary aerosol-generating procedures in a negative-pressure room, also known as an airborne infection isolation room (AIIR), when available **(AIII)**.
- The Panel recognizes that aerosol-generating procedures are necessary to perform in some patients, and that such procedures can be carried out with a high degree of safety if infection control guidelines are followed.

Rationale

AIIRs lower the risk of cross-contamination among rooms and lower the risk of infection for staff and patients outside the room when aerosol-generating procedures are performed. AIIRs were effective in preventing virus spread during the SARS epidemic.² If an AIIR is not available, a high-efficiency particulate air (HEPA) filter should be used, especially for patients on high-flow nasal cannula or noninvasive ventilation. HEPA filters reduce virus transmission in simulations.⁵

Recommendations

- For health care workers who are providing usual care for non-ventilated patients with COVID-19, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator) or a surgical mask, in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield

or safety goggles) (**AII**).

- For health care workers who are performing non-aerosol-generating procedures on patients with COVID-19 who are on closed-circuit mechanical ventilation, the Panel recommends using an N95 respirator (or equivalent or higher-level respirator), in addition to other PPE (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) because ventilator circuits may become disrupted unexpectedly (**BIII**).

Rationale

There is evidence from viral diseases, including SARS, that both surgical masks and N95 masks reduce transmission of infection.⁶ Current evidence suggests that surgical masks are probably not inferior to N95 respirators for preventing transmission of laboratory-confirmed, seasonal respiratory viral infections (e.g., influenza).^{7,8} A recent systematic review and meta-analysis of randomized controlled trials that compared the protective effect of medical masks with N95 respirators demonstrated that the use of medical masks did not increase laboratory-confirmed viral (including coronavirus) respiratory infection or clinical respiratory illness.⁹

Recommendations

- The Panel recommends that endotracheal intubation in patients with COVID-19 be performed by health care providers with extensive airway management experience, if possible (**AIII**).
- The Panel recommends that intubation be performed using video laryngoscopy, if possible (**CIII**).

Rationale

Practices that maximize the chances of first-pass success and minimize aerosolization should be used when intubating patients with suspected or confirmed COVID-19.^{10,11} Thus, the Panel recommends that the health care worker with the most experience and skill in airway management be the first to attempt intubation. The close facial proximity of direct laryngoscopy can expose health care providers to higher concentrations of viral aerosols. It is also important to avoid having unnecessary staff in the room during intubation procedures.

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Hemodynamics

Last Updated: October 9, 2020

Most of the hemodynamic recommendations below are similar to those previously published in the *Surviving Sepsis Campaign: International Guidelines for Management of Sepsis and Septic Shock: 2016*. Ultimately, patients with COVID-19 who require fluid resuscitation or hemodynamic management of shock should be treated and managed identically to patients with septic shock.¹

COVID-19 patients who require fluid resuscitation or hemodynamic management of shock should be treated and managed for septic shock in accordance with other published guidelines, with the following exceptions.

Recommendation

- For adults with COVID-19 and shock, the COVID-19 Treatment Guidelines Panel (the Panel) recommends using dynamic parameters, skin temperature, capillary refilling time, and/or lactate levels over static parameters to assess fluid responsiveness (**BII**).

Rationale

No direct evidence addresses the optimal resuscitation strategy for patients with COVID-19 and shock. In a systematic review and meta-analysis of 13 non-COVID-19 randomized clinical trials (n = 1,652),² dynamic assessment to guide fluid therapy reduced mortality (risk ratio 0.59; 95% CI, 0.42–0.83), intensive care unit (ICU) length of stay (weighted mean difference -1.16 days; 95% CI, -1.97 to -0.36), and duration of mechanical ventilation (weighted mean difference -2.98 hours; 95% CI, -5.08 to -0.89). Dynamic parameters used in these trials included stroke volume variation (SVV), pulse pressure variation (PPV), and stroke volume change with passive leg raise or fluid challenge. Passive leg raising, followed by PPV and SVV, appears to predict fluid responsiveness with the highest accuracy.³ The static parameters included components of early goal-directed therapy (e.g., central venous pressure, mean arterial pressure).

Resuscitation of non-COVID-19 patients with shock based on serum lactate levels has been summarized in a systematic review and meta-analysis of seven randomized clinical trials (n = 1,301). Compared with central venous oxygen saturation-guided therapy, early lactate clearance-directed therapy was associated with a reduction in mortality (relative ratio 0.68; 95% CI, 0.56–0.82), shorter length of ICU stay (mean difference -1.64 days; 95% CI, -3.23 to -0.05), and shorter duration of mechanical ventilation (mean difference -10.22 hours; 95% CI, -15.94 to -4.50).⁴

Recommendation

- For the acute resuscitation of adults with COVID-19 and shock, the Panel recommends using buffered/balanced crystalloids over unbalanced crystalloids (**BII**).

Rationale

A pragmatic randomized trial that compared balanced and unbalanced crystalloids in 15,802 critically ill adults found that the rate of the composite outcome of death, new renal-replacement therapy, or persistent renal dysfunction was lower in the balanced crystalloids group (OR 0.90; 95% CI, 0.82–0.99; $P = 0.04$).⁵ A secondary analysis compared outcomes in a subset of patients with sepsis (n = 1,641). Among the sepsis patients in the balanced crystalloids group, there were fewer deaths (aOR 0.74; 95% CI, 0.59–0.93; $P = 0.01$), as well as fewer days requiring vasopressors and renal replacement therapy.⁶ A subsequent meta-analysis of 21 randomized controlled trials (n = 20,213) that included the pragmatic

trial cited above compared balanced crystalloids to 0.9% saline for resuscitation of critically ill adults and children and reported nonsignificant differences in hospital mortality (OR 0.91; 95% CI, 0.83–1.01) and acute kidney injury (OR 0.92; 95% CI, 0.84–1.00).⁷

Recommendation

- For the acute resuscitation of adults with COVID-19 and shock, the Panel **recommends against** the initial use of albumin for resuscitation (**BI**).

Rationale

A meta-analysis of 20 non-COVID-19 randomized controlled trials (n = 13,047) that compared the use of albumin or fresh-frozen plasma to crystalloids in critically ill patients found no difference in all-cause mortality,⁸ whereas a meta-analysis of 17 non-COVID-19 randomized controlled trials (n = 1,977) that compared the use of albumin to crystalloids specifically in patients with sepsis observed a reduction in mortality (OR 0.82; 95% CI, 0.67–1.0; *P* = 0.047).⁹ Given the higher cost of albumin and the lack of a definitive clinical benefit, the Panel **recommends against** the routine use of albumin for initial acute resuscitation of patients with COVID-19 and shock.

Additional Recommendations Based on General Principles of Critical Care

- The Panel **recommends against** using hydroxyethyl starches for intravascular volume replacement in patients with sepsis or septic shock (**AI**).
- The Panel recommends norepinephrine as the first-choice vasopressor (**AII**). The Panel recommends adding either vasopressin (up to 0.03 units/minute) (**BII**) or epinephrine (**CII**) to norepinephrine to raise mean arterial pressure to target or adding vasopressin (up to 0.03 units/minute) (**CII**) to decrease norepinephrine dosage.
- When norepinephrine is available, the Panel **recommends against** using dopamine for patients with COVID-19 and shock (**AI**).
- The Panel **recommends against** using low-dose dopamine for renal protection (**BII**).
- The Panel recommends using dobutamine in patients who show evidence of cardiac dysfunction and persistent hypoperfusion despite adequate fluid loading and the use of vasopressor agents (**BII**).
- The Panel recommends that all patients who require vasopressors have an arterial catheter placed as soon as practical, if resources are available (**BIII**).
- For adults with COVID-19 and refractory septic shock who are not receiving corticosteroids to treat their COVID-19, the Panel recommends using low-dose corticosteroid therapy (“shock-reversal”) over no corticosteroid therapy (**BII**).
- A typical corticosteroid regimen in septic shock is intravenous hydrocortisone 200 mg per day administered either as an infusion or in intermittent doses. The duration of hydrocortisone therapy is usually a clinical decision.
- Patients who are receiving corticosteroids for COVID-19 are receiving sufficient replacement therapy such that they do not require additional hydrocortisone.

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Oxygenation and Ventilation

Last Updated: December 17, 2020

The COVID-19 Treatment Guidelines Panel's (the Panel's) recommendations below emphasize recommendations from the Surviving Sepsis Campaign Guidelines for [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#).

Nonmechanically Ventilated Adults With Hypoxemic Respiratory Failure

Recommendations

- For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the Panel recommends high-flow nasal cannula (HFNC) oxygen over noninvasive positive pressure ventilation (NIPPV) (**BI**).
- In the absence of an indication for endotracheal intubation, the Panel recommends a closely monitored trial of NIPPV for adults with COVID-19 and acute hypoxemic respiratory failure and for whom HFNC is not available (**BIII**).
- For patients with persistent hypoxemia despite increasing supplemental oxygen requirements in whom endotracheal intubation is not otherwise indicated, the Panel recommends considering a trial of awake prone positioning to improve oxygenation (**CIII**).
- The Panel **recommends against** using awake prone positioning as a rescue therapy for refractory hypoxemia to avoid intubation in patients who otherwise meet the indications for intubation and mechanical ventilation (**AIII**).
- If intubation becomes necessary, the procedure should be performed by an experienced practitioner in a controlled setting due to the enhanced risk of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) exposure to health care practitioners during intubation (**AII**).

Rationale

Severe illness in COVID-19 typically occurs approximately 1 week after the onset of symptoms. The most common symptom is dyspnea, which is often accompanied by hypoxemia. Patients with severe disease typically require supplemental oxygen and should be monitored closely for worsening respiratory status because some patients may progress to acute respiratory distress syndrome (ARDS).

Goal of Oxygenation

The optimal oxygen saturation (SpO₂) in adults with COVID-19 is uncertain. However, a target SpO₂ of 92% to 96% seems logical considering that indirect evidence from experience in patients without COVID-19 suggests that an SpO₂ <92% or >96% may be harmful.

Regarding the potential harm of maintaining an SpO₂ <92%, a trial randomly assigned ARDS patients without COVID-19 to either a conservative oxygen strategy (target SpO₂ of 88% to 92%) or a liberal oxygen strategy (target SpO₂ ≥96%). The trial was stopped early due to futility after enrolling 205 patients, but in the conservative oxygen group there was increased mortality at 90 days (between-group risk difference of 14%; 95% CI, 0.7% to 27%) and a trend toward increased mortality at 28-days (between-group risk difference of 8%; 95% CI, -5% to 21%).¹

Regarding the potential harm of maintaining an SpO₂ >96%, a meta-analysis of 25 randomized trials involving patients without COVID-19 found that a liberal oxygen strategy (median SpO₂ of 96%) was associated with an increased risk of in-hospital mortality compared to a lower SpO₂ comparator (relative risk 1.21; 95% CI, 1.03–1.43).²

Acute Hypoxemic Respiratory Failure

In adults with COVID-19 and acute hypoxemic respiratory failure, conventional oxygen therapy may be insufficient to meet the oxygen needs of the patient. Options for providing enhanced respiratory support include HFNC, NIPPV, intubation and invasive mechanical ventilation, or extracorporeal membrane oxygenation (ECMO).

High-Flow Nasal Cannula and Noninvasive Positive Pressure Ventilation

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial in patients without COVID-19 who had acute hypoxemic respiratory failure. Study participants were randomized to HFNC, conventional oxygen therapy, or NIPPV. The patients in the HFNC group had more ventilator-free days (24 days) than those in the conventional oxygen therapy group (22 days) or NIPPV group (19 days) ($P = 0.02$), and 90-day mortality was lower in the HFNC group than in either the conventional oxygen therapy group (HR 2.01; 95% CI, 1.01–3.99) or the NIPPV group (HR 2.50; 95% CI, 1.31–4.78).³ In the subgroup of more severely hypoxemic patients ($\text{PaO}_2/\text{FiO}_2$ mm Hg ≤ 200), the intubation rate was lower for HFNC than for conventional oxygen therapy or NIPPV (HR 2.07 and 2.57, respectively).

The trial's findings were corroborated by a meta-analysis of eight trials with 1,084 patients conducted to assess the effectiveness of oxygenation strategies prior to intubation. Compared to NIPPV, HFNC reduced the rate of intubation (OR 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63).⁴

NIPPV may generate aerosol spread of SARS-CoV-2 and thus increase nosocomial transmission of the infection.^{5,6} It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission than NIPPV.

Prone Positioning for Nonintubated Patients

Although prone positioning has been shown to improve oxygenation and outcomes in patients with moderate-to-severe ARDS who are receiving mechanical ventilation,^{7,8} there is less evidence regarding the benefit of prone positioning in awake patients who require supplemental oxygen without mechanical ventilation. In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department, awake prone positioning improved the overall median oxygen saturation of the patients. However, 13 patients still required intubation due to respiratory failure within 24 hours of presentation to the emergency department.⁹ Other case series of patients with COVID-19 requiring oxygen or NIPPV have similarly reported that awake prone positioning is well-tolerated and improves oxygenation,¹⁰⁻¹² with some series also reporting low intubation rates after proning.^{10,12}

A prospective feasibility study of awake prone positioning in 56 patients with COVID-19 receiving HFNC or NIPPV in a single Italian hospital found that prone positioning for ≤ 3 hours was feasible in 84% of the patients. There was a significant improvement in oxygenation during prone positioning ($\text{PaO}_2/\text{FiO}_2$ 181 mm Hg in supine position vs. $\text{PaO}_2/\text{FiO}_2$ 286 mm Hg in prone position). However, when compared with baseline oxygenation before initiation of prone positioning, this improvement in oxygenation was not sustained ($\text{PaO}_2/\text{FiO}_2$ of 181 mm Hg and 192 mm Hg at baseline and 1 hour after resupination, respectively). Among patients put in the prone position, there was no difference in intubation rate between patients who maintained improved oxygenation (i.e., responders) and nonresponders.⁹

A prospective, multicenter observational cohort study in Spain and Andorra evaluated the effect of prone positioning on the rate of intubation in COVID-19 patients with acute respiratory failure receiving HFNC. Of the 199 patients requiring HFNC, 55 (27.6%) were treated with prone positioning. Although the time to intubation was 1 day (IQR 1.0–2.5) in patients receiving HFNC and prone positioning versus

2 days [IQR 1.0–3.0] in patients receiving only HFNC ($P = 0.055$), the use of awake prone positioning did not reduce the risk of intubation (RR 0.87; 95% CI, 0.53–1.43; $P = 0.60$).¹³

Overall, despite promising data, it is unclear which hypoxemic, nonintubated patients with COVID-19 pneumonia benefit from prone positioning, how long prone positioning should be continued, or whether the technique prevents the need for intubation or improves survival.¹⁰

Appropriate candidates for awake prone positioning are those who can adjust their position independently and tolerate lying prone. Awake prone positioning is **contraindicated** in patients who are in respiratory distress and who require immediate intubation. Awake prone positioning is also **contraindicated** in patients who are hemodynamically unstable, patients who recently had abdominal surgery, and patients who have an unstable spine.¹⁴ Awake prone positioning is acceptable and feasible for pregnant patients and can be performed in the left lateral decubitus position or the fully prone position.¹⁵

Intubation for Invasive Mechanical Ventilation

It is essential to monitor hypoxemic patients with COVID-19 closely for signs of respiratory decompensation. To ensure the safety of both patients and health care workers, intubation should be performed in a controlled setting by an experienced practitioner.

Mechanically Ventilated Adults

Recommendations

For mechanically ventilated adults with COVID-19 and ARDS:

- The Panel recommends using low tidal volume (VT) ventilation (VT 4–8 mL/kg of predicted body weight) over higher VT ventilation (VT >8 mL/kg) (**AI**).
- The Panel recommends targeting plateau pressures of <30 cm H₂O (**AII**).
- The Panel recommends using a conservative fluid strategy over a liberal fluid strategy (**BII**).
- The Panel **recommends against** the routine use of inhaled nitric oxide (**AI**).

Rationale

There is no evidence that ventilator management of patients with hypoxemic respiratory failure due to COVID-19 should differ from ventilator management of patients with hypoxemic respiratory failure due to other causes.

Positive End-Expiratory Pressure and Prone Positioning in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome

Recommendations

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

- The Panel recommends using a higher positive end-expiratory pressure (PEEP) strategy over a lower PEEP strategy (**BII**).
- For mechanically ventilated adults with COVID-19 and refractory hypoxemia despite optimized ventilation, the Panel recommends prone ventilation for 12 to 16 hours per day over no prone ventilation (**BII**).

Rationale

PEEP is beneficial in patients with ARDS because it prevents alveolar collapse, improves oxygenation, COVID-19 Treatment Guidelines

and minimizes atelectotrauma, a source of ventilator-induced lung injury. A meta-analysis of individual patient data from the three largest trials that compared lower and higher levels of PEEP in patients without COVID-19 found lower rates of ICU mortality and in-hospital mortality with higher PEEP in those with moderate ($\text{PaO}_2/\text{FiO}_2$ 100–200 mm Hg) and severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 100$ mm Hg).¹⁶

Although there is no clear standard as to what constitutes a high level of PEEP, one conventional threshold is >10 cm H_2O .¹⁷ Recent reports have suggested that, in contrast to patients with non-COVID-19 causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static lung compliance and thus, in these patients, higher PEEP levels may cause harm by compromising hemodynamics and cardiovascular performance.^{18,19} Other studies reported that patients with moderate to severe ARDS due to COVID-19 had low compliance, similar to the lung compliance seen in patients with conventional ARDS.²⁰⁻²³ These seemingly contradictory observations suggest that COVID-19 patients with ARDS are a heterogeneous population and assessment for responsiveness to higher PEEP should be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as barotrauma and hypotension.

Neuromuscular Blockade in Mechanically Ventilated Adults With Moderate to Severe Acute Respiratory Distress Syndrome

Recommendations

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

- The Panel recommends using, as needed, intermittent boluses of neuromuscular blocking agents (NMBA) or continuous NMBA infusion to facilitate protective lung ventilation (**BIII**).
- In the event of persistent patient-ventilator dyssynchrony, or in cases where a patient requires ongoing deep sedation, prone ventilation, or persistently high plateau pressures, the Panel recommends using a continuous NMBA infusion for up to 48 hours as long as patient anxiety and pain can be adequately monitored and controlled (**BIII**).

Rationale

The recommendation for intermittent boluses of NMBA or continuous infusion of NMBA to facilitate lung protection may require a health care provider to enter the patient's room frequently for close clinical monitoring. Therefore, in some situations, the risks of SARS-CoV-2 exposure and the need to use personal protective equipment for each entry into a patient's room may outweigh the benefit of NMBA treatment.

Rescue Therapies for Mechanically Ventilated Adults With Acute Respiratory Distress Syndrome

Recommendations

For mechanically ventilated adults with COVID-19, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies:

- The Panel recommends using recruitment maneuvers rather than not using recruitment maneuvers (**CII**).
- If recruitment maneuvers are used, the Panel **recommends against** using staircase (incremental PEEP) recruitment maneuvers (**AII**).
- The Panel recommends using an inhaled pulmonary vasodilator as a rescue therapy; if no rapid improvement in oxygenation is observed, the treatment should be tapered off (**CIII**).

Rationale

There are no studies to date assessing the effect of recruitment maneuvers on oxygenation in severe ARDS due to COVID-19. However, a systematic review and meta-analysis of six trials of recruitment maneuvers in non-COVID-19 patients with ARDS found that recruitment maneuvers reduced mortality, improved oxygenation 24 hours after the maneuver, and decreased the need for rescue therapy.²⁴ Because recruitment maneuvers can cause barotrauma or hypotension, patients should be closely monitored during recruitment maneuvers. If a patient decompensates during recruitment maneuvers, the maneuver should be stopped immediately. The importance of properly performing recruitment maneuvers was illustrated by an analysis of eight randomized controlled trials in non-COVID-19 patients (n = 2,544) which found that recruitment maneuvers did not reduce hospital mortality (RR 0.90; 95% CI, 0.78–1.04). Subgroup analysis found that traditional recruitment maneuvers significantly reduced hospital mortality (RR 0.85; 95% CI, 0.75–0.97), whereas incremental PEEP titration recruitment maneuvers increased mortality (RR 1.06; 95% CI, 0.97–1.17).²⁵

Although there are no published studies of inhaled nitric oxide in patients with COVID-19, a Cochrane review of 13 trials of inhaled nitric oxide use in patients with ARDS found no mortality benefit.²⁶ Because the review showed a transient benefit in oxygenation, it is reasonable to attempt inhaled nitric oxide as a rescue therapy in COVID patients with severe ARDS after other options have failed. However, if there is no benefit in oxygenation with inhaled nitric oxide, it should be tapered quickly to avoid rebound pulmonary vasoconstriction that may occur with discontinuation after prolonged use.

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Acute Kidney Injury and Renal Replacement Therapy

Last Updated: December 17, 2020

Recommendations

- For critically ill patients with COVID-19 who have acute kidney injury (AKI) and who develop indications for renal replacement therapy (RRT), the COVID-19 Treatment Guidelines Panel (the Panel) recommends continuous renal replacement therapy (CRRT), if available **(BIII)**.
- If CRRT is not available or not possible due to limited resources, the Panel recommends prolonged intermittent renal replacement therapy (PIRRT) rather than intermittent hemodialysis (IHD) **(BIII)**.

Rationale

AKI that requires RRT occurs in approximately 22% of patients with COVID-19 who are admitted to the intensive care unit.¹ Evidence pertaining to RRT in patients with COVID-19 is scarce. Until additional evidence is available, the Panel suggests using the same indications for RRT in patients with COVID-19 as those used for other critically ill patients.²

RRT modalities have not been compared in COVID-19 patients; the Panel's recommendations are motivated by the desire to minimize the risk of viral transmission to health care workers. The Panel considers CRRT to be the preferred RRT modality. CRRT is preferable to PIRRT because medication dosing for CRRT is more easily optimized and CRRT does not require nursing staff to enter the patient's room to begin and end dialysis sessions. CRRT and PIRRT are both preferable to IHD because neither requires a dedicated hemodialysis nurse.³ Peritoneal dialysis has also been used during surge situations in patients with COVID-19.

In situations where there may be insufficient CRRT machines or equipment to meet demand, the Panel advocates performing PIRRT instead of CRRT, and then using the machine for another patient after appropriate cleaning.

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Pharmacologic Interventions

Last Updated: October 9, 2020

Antiviral Therapy

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of remdesivir with or without corticosteroids.

Immune-Based Therapy

Several immune-based therapies that are expected to modify the course of COVID-19, including corticosteroids, are currently under investigation or are already in use. These agents may target the virus (e.g., convalescent plasma) or modulate the immune response (e.g., corticosteroids, interleukin [IL]-1 or IL-6 inhibitors). Recommendations regarding immune-based therapy can be found in [Immune-Based Therapy Under Evaluation for the Treatment of COVID-19](#).

Corticosteroids

See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of dexamethasone with or without remdesivir.

Adjunctive Therapy

Recommendations regarding adjunctive therapy used in the critical care setting, including antithrombotic therapy and vitamin C, can be found in the [Adjunctive Therapy](#) section.

Empiric Broad-Spectrum Antimicrobial Therapy

Recommendations

- In patients with COVID-19 and severe or critical illness, there are insufficient data to recommend empiric broad-spectrum antimicrobial therapy in the absence of another indication.
- If antimicrobials are initiated, the Panel recommends that their use should be reassessed daily in order to minimize the adverse consequences of unnecessary antimicrobial therapy (**AIII**).

Rationale

There are no reliable estimates of the incidence or prevalence of copathogens with severe acute respiratory syndrome coronavirus 2 at this time.

Some experts routinely administer broad-spectrum antibiotics as empiric therapy for bacterial pneumonia to all patients with COVID-19 and moderate or severe hypoxemia. Other experts administer antibiotics only for specific situations, such as the presence of a lobar infiltrate on a chest X-ray, leukocytosis, an elevated serum lactate level, microbiologic data, or shock.

Gram stain, culture, or other testing of respiratory specimens is often not available due to concerns about aerosolization of the virus during diagnostic procedures or when processing specimens.

There are no clinical trials that have evaluated the use of empiric antimicrobial agents in patients with COVID-19 or other severe coronavirus infections.

Extracorporeal Membrane Oxygenation

Last Updated: December 17, 2020

Recommendation

- There are insufficient data to recommend either for or against the use of extracorporeal membrane oxygenation (ECMO) in patients with COVID-19 and refractory hypoxemia.

Rationale

ECMO has been used as a short-term rescue therapy in patients with acute respiratory distress syndrome (ARDS) caused by COVID-19 and refractory hypoxemia. However, there is no conclusive evidence that ECMO is responsible for better clinical outcomes regardless of the cause of hypoxemic respiratory failure.¹⁻⁴

The clinical outcomes for patients with ARDS who are treated with ECMO are variable and depend on multiple factors, including the etiology of hypoxemic respiratory failure, the severity of pulmonary and extrapulmonary illness, the presence of comorbidities, and the ECMO experience of the individual center.⁵⁻⁷ A recent case series of 83 COVID-19 patients in Paris reported a 60-day mortality of 31% for patients on ECMO.⁸ This mortality was similar to the mortality observed in a 2018 study of non-COVID-19 patients with ARDS who were treated with ECMO during the ECMO to Rescue Lung Injury in Severe ARDS (EOLIA) trial; that study reported a mortality of 35% at Day 60.³

The Extracorporeal Life Support Organization (ELSO) Registry provides the largest multicenter outcome dataset of patients with confirmed COVID-19 who received ECMO support and whose data were voluntarily submitted. A recent cohort study evaluated ELSO Registry data for 1,035 COVID-19 patients who initiated ECMO between January 16 and May 1, 2020, at 213 hospitals in 36 countries. This study reported an estimated cumulative in-hospital mortality of 37.4% in these patients 90 days after they initiated ECMO (95% CI; 34.4% to 40.4%).⁹ Without a controlled trial that evaluates the use of ECMO in patients with COVID-19 and hypoxemic respiratory failure (e.g., ARDS), the benefits of ECMO cannot be clearly defined for this patient population.

Ideally, clinicians who are interested in using ECMO should try to enter their patients into clinical trials or clinical registries so that more informative data can be obtained. The following resources provide more information on the use of ECMO in patients with COVID-19:

- [The ELSO ECMO in COVID-19 website](#)
- A list of [clinical trials that are evaluating ECMO in patients with COVID-19](#) on [ClinicalTrials.gov](#)

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