

Care of Critically Ill Patients With COVID-19

Last Updated: October 9, 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 (i.e., gloves, gown, and eye protection such as a face shield or safety goggles) **(AIII)**.
- 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)**.

Hemodynamic Support:

- The Panel recommends norepinephrine as the first-choice vasopressor **(AII)**.
- 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)**.

Ventilatory Support:

- 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 for whom HFNC is not available **(BIII)**.
- For adults with COVID-19 who are receiving supplemental oxygen, the Panel recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting **(AII)**.
- 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 require intubation and mechanical ventilation **(AIII)**.
- 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 tidal volumes (VT >8 mL/kg) **(AI)**.
- 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, severe ARDS, and hypoxemia despite optimized ventilation and other rescue strategies, 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)**.
- There are insufficient data to recommend either for or against the routine use of extracorporeal membrane oxygenation (ECMO) for patients with COVID-19 and refractory hypoxemia.

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:

- See [Therapeutic Management of Patients with COVID-19](#) for recommendations on the use of dexamethasone and remdesivir, either alone or in combination.

- 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.

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

Last Updated: October 9, 2020

Severe cases of COVID-19 may be associated with acute respiratory distress syndrome, septic shock, cardiac dysfunction, elevations 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.

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, although special precaution to prevent environmental contamination by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is warranted.

As with any patient in the intensive care unit (ICU), successful clinical management of a patient with COVID-19 depends on attention to the primary process leading to the ICU admission, but also to underlying comorbidities and nosocomial complications.

Comorbid Conditions

Certain attributes and comorbidities, such as older age, cardiovascular disease, diabetes, chronic obstructive pulmonary disease, cancer, renal disease, obesity, sickle cell disease, and 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. For the treatment of shock, however, empiric broad-spectrum antimicrobial therapy is the standard of care. 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

There is a growing body of literature relating COVID-19 to myocarditis and pericardial dysfunction in approximately 20% of patients.^{4,6,9-12} Acute cardiac injury and arrhythmias have also been described in patients with COVID-19.

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.¹³⁻¹⁵ Autopsy studies provide additional evidence of both thromboembolic disease and microvascular thrombosis in patients with COVID-19.¹⁶ Some authors have called for routine surveillance of ICU patients for venous thromboembolism.¹⁷ Please refer to [Antithrombotic Therapy in Patients with COVID-19](#) 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 [Acute Kidney Injury and Renal Replacement Therapy](#) 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.¹⁸⁻²³ The risk factors for severe COVID-19 in children have not yet been established. Based on data from studies of adults and extrapolation from data on other pediatric respiratory viruses, 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.^{24,25} 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 criteria for typical or atypical Kawasaki disease. For details on MIS-C clinical features and the treatments that are being investigated, see [Special Considerations in Children](#).

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 the multiprofessional ICU team with recommendations on the prevention, detection, and treatment of pain, sedation, and delirium.^{26,27} Sedation management strategies such as maintaining a light level of sedation, when appropriate, and minimizing sedative exposure have shortened duration of mechanical ventilation and ICU length of stay in patients without COVID-19.^{28,29}

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 tool also provides frontline staff with practical application strategies for each element.³⁰ Incorporating the A-F Bundle using an interprofessional team model helps standardize communication among the treatment team members and improve survival and reduce long-term cognitive dysfunction of patients.³¹ Despite the known benefits of the A-F Bundle, its impact has not been directly assessed in patients with COVID-19; however, 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 impede routine implementation of the [PADIS Guidelines](#) forcing a return to older sedatives with prolonged duration of action and active metabolites, thereby putting these 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.³² Neurological complications are associated with older age and with underlying conditions, such as hypertension and diabetes mellitus.³³ Autopsy studies demonstrate macrovascular, as well as microvascular thrombosis, with evidence of hypoxic ischemia.³⁴ 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.³⁵ 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.³⁶⁻³⁸ Cognitive dysfunction affects 30% to 80% of patients discharged from the ICU.³⁹⁻⁴¹ About 50% of ICU survivors do not return to work within 1 year after discharge.⁴² Although no single risk factor has been associated with PICS, there are opportunities to minimize the risk of PICS through medication management (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.⁴³ Early reports suggest that some patients with COVID-19 who have been treated in the ICU express manifestations of PICS.⁴⁴ 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 in order 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 front-line 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 present barriers to communication with 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.

Acknowledgments

The Surviving Sepsis Campaign (SSC), an initiative supported by the SCCM and the European Society of Intensive Care Medicine, issued *Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19)* in March 2020.¹ The COVID-19 Treatment Guidelines Panel (the Panel) has based the recommendations in this section on the SSC COVID-19 Guidelines with permission, and the Panel gratefully acknowledges the work of the SSC COVID-19 Guidelines Panel. The Panel also acknowledges the contributions and expertise of Andrew Rhodes, MBBS, MD, of St. George's University Hospitals in London, England, and Waleed Alhazzani, MBBS, MSc, of McMaster University in Hamilton, Canada.

References

1. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
2. Centers for Disease Control and Prevention. Evidence used to update the list of underlying medical conditions that increase a person's risk of severe illness from COVID-19. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/need-extra-precautions/evidence-table.html>. Accessed September 22, 2020.
3. Wu C, Chen X, Cai Y, et al. Risk factors associated with acute respiratory distress syndrome and death in patients with coronavirus disease 2019 pneumonia in Wuhan, China. *JAMA Intern Med*. 2020;180(7):934-943. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32167524>.
4. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington state. *JAMA*. 2020;323(16):1612-1614. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32191259>.
5. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. COVID-19 in critically ill patients in the Seattle region—case series. *N Engl J Med*. 2020;382(21):2012-2022. Available at: <https://www.ncbi.nlm.nih.gov/>

pubmed/32227758.

6. Yang X, Yu Y, Xu J, et al. Clinical course and outcomes of critically ill patients with SARS-CoV-2 pneumonia in Wuhan, China: a single-centered, retrospective, observational study. *Lancet Respir Med*. 2020;8(5):475-481. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32105632>.
7. Chen T, Wu D, Chen H, et al. Clinical characteristics of 113 deceased patients with coronavirus disease 2019: retrospective study. *BMJ*. 2020;368:m1091. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32217556>.
8. Du Y, Tu L, Zhu P, et al. Clinical features of 85 fatal cases of COVID-19 from Wuhan: a retrospective observational study. *Am J Respir Crit Care Med*. 2020;201(11):1372-1379. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32242738>.
9. Shi S, Qin M, Shen B, et al. Association of cardiac injury with mortality in hospitalized patients with COVID-19 in Wuhan, China. *JAMA Cardiol*. 2020;5(7):802-810. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32211816>.
10. Huang C, Wang Y, Li X, et al. Clinical features of patients infected with 2019 novel coronavirus in Wuhan, China. *Lancet*. 2020;395(10223):497-506. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31986264>.
11. Zhou F, Yu T, Du R, et al. Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *Lancet*. 2020;395(10229):1054-1062. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32171076>.
12. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020;323(11):1061-1069. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32031570>.
13. Llitjos JF, Leclerc M, Chochois C, et al. High incidence of venous thromboembolic events in anticoagulated severe COVID-19 patients. *J Thromb Haemost*. 2020;18(7):1743-1746. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320517>.
14. Helms J, Tacquard C, Severac F, et al. High risk of thrombosis in patients in severe SARS-CoV-2 infection: a multicenter prospective cohort study. *Intensive Care Med*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7197634/>.
15. Klok FA, Kruip M, van der Meer NJM, et al. Incidence of thrombotic complications in critically ill ICU patients with COVID-19. *Thromb Res*. 2020;191:145-147. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32291094>.
16. Menter T, Haslbauer JD, Nienhold R, et al. Post-mortem examination of COVID19 patients reveals diffuse alveolar damage with severe capillary congestion and variegated findings of lungs and other organs suggesting vascular dysfunction. *Histopathology*. 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32364264>.
17. Tavazzi G, Civardi L, Caneva L, Mongodi S, Mojoli F. Thrombotic events in SARS-CoV-2 patients: an urgent call for ultrasound screening. *Intensive Care Med*. 2020;46(6):1121-1123. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32322918>.
18. Sun D, Li H, Lu XX, et al. Clinical features of severe pediatric patients with coronavirus disease 2019 in Wuhan: a single center's observational study. *World J Pediatr*. 2020;16(3):251-259. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32193831>.
19. Dong Y, Mo X, Hu Y, et al. Epidemiological characteristics of 2,143 pediatric patients with 2019 coronavirus disease in China. *Pediatrics*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32179660>.
20. Centers for Disease Control and Prevention. Coronavirus Disease 2019 in Children — United States, February 12–April 2, 2020. 2020. Available at: <https://www.cdc.gov/mmwr/volumes/69/wr/mm6914e4.htm>. Accessed September 29, 2020.
21. Chao JY, Derespina KR, Herold BC, et al. Clinical characteristics and outcomes of hospitalized and critically ill children and adolescents with coronavirus disease 2019 (COVID-19) at a tertiary care medical center in New York City. *J Pediatr*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32407719>.

22. Zachariah P, Johnson CL, Halabi KC, et al. Epidemiology, Clinical Features, and Disease Severity in Patients With Coronavirus Disease 2019 (COVID-19) in a Children's Hospital in New York City, New York. *JAMA Pediatr.* 2020; Published online ahead of print. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32492092>.
23. DeBiasi RL, Song X, Delaney M, et al. Severe COVID-19 in children and young adults in the Washington, DC metropolitan region. *J Pediatr.* 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32405091>.
24. Whittaker E, Bamford A, Kenny J, et al. Clinical characteristics of 58 children with a pediatric inflammatory multisystem syndrome temporally associated with SARS-CoV-2. *JAMA.* 2020 ;324(3):259-269. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32511692>.
25. Verdoni L, Mazza A, Gervasoni A, et al. An outbreak of severe Kawasaki-like disease at the Italian epicentre of the SARS-CoV-2 epidemic: an observational cohort study. *Lancet.* 2020;395(10239):1771-1778. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32410760>.
26. Barr J, Fraser GL, Puntillo K, et al. Clinical practice guidelines for the management of pain, agitation, and delirium in adult patients in the intensive care unit. *Crit Care Med.* 2013;41(1):263-306. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23269131>.
27. Devlin JW, Skrobik Y, Gelinas C, et al. Clinical practice guidelines for the prevention and management of pain, agitation/sedation, delirium, immobility, and sleep disruption in adult patients in the ICU. *Crit Care Med.* 2018;46(9):e825-e873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30113379>.
28. Kress JP, Vinayak AG, Levitt J, et al. Daily sedative interruption in mechanically ventilated patients at risk for coronary artery disease. *Crit Care Med.* 2007;35(2):365-371. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17205005>.
29. Girard TD, Kress JP, Fuchs BD, et al. Efficacy and safety of a paired sedation and ventilator weaning protocol for mechanically ventilated patients in intensive care (Awakening and Breathing Controlled trial): a randomised controlled trial. *Lancet.* 2008;371(9607):126-134. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18191684>.
30. Society of Critical Care Medicine. ICU Liberation Bundle (A-F). Available at: <https://www.sccm.org/ICULiberation/ABCDEF-Bundles>. Accessed September 22, 2020.
31. Barnes-Daly MA, Phillips G, Ely EW. Improving hospital survival and reducing brain dysfunction at seven California community hospitals: implementing PAD guidelines via the ABCDEF bundle in 6,064 patients. *Crit Care Med.* 2017;45(2):171-178. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27861180>.
32. Helms J, Kremer S, Merdji H, et al. Neurologic Features in Severe SARS-CoV-2 Infection. *N Engl J Med.* 2020;382(23):2268-2270. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32294339>.
33. Mao L, Jin H, Wang M, et al. Neurologic Manifestations of Hospitalized Patients With Coronavirus Disease 2019 in Wuhan, China. *JAMA Neurol.* 2020;77(6):683-690. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32275288>.
34. Solomon IH, Normandin E, Bhattacharyya S, et al. Neuropathological features of COVID-19. *N Engl J Med.* 2020;383(10):989-992. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32530583>.
35. Society of Critical Care Medicine. Post-intensive care syndrome. 2013. Available at: <https://www.sccm.org/MyICUCare/THRIVE/Post-intensive-Care-Syndrome>. Accessed September 22, 2020.
36. Fan E, Dowdy DW, Colantuoni E, et al. Physical complications in acute lung injury survivors: a two-year longitudinal prospective study. *Crit Care Med.* 2014;42(4):849-859. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24247473>.
37. De Jonghe B, Sharshar T, Lefaucheur JP, et al. Paresis acquired in the intensive care unit: a prospective multicenter study. *JAMA.* 2002;288(22):2859-2867. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12472328>.
38. Ali NA, O'Brien JM, Jr., Hoffmann SP, et al. Acquired weakness, handgrip strength, and mortality in critically ill patients. *Am J Respir Crit Care Med.* 2008;178(3):261-268. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/18511703>.

39. Pandharipande PP, Girard TD, Jackson JC, et al. Long-term cognitive impairment after critical illness. *N Engl J Med*. 2013;369(14):1306-1316. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/24088092>.
40. Iwashyna TJ, Ely EW, Smith DM, Langa KM. Long-term cognitive impairment and functional disability among survivors of severe sepsis. *JAMA*. 2010;304(16):1787-1794. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20978258>.
41. Mikkelsen ME, Christie JD, Lanken PN, et al. The adult respiratory distress syndrome cognitive outcomes study: long-term neuropsychological function in survivors of acute lung injury. *Am J Respir Crit Care Med*. 2012;185(12):1307-1315. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22492988>.
42. Kamdar BB, Sepulveda KA, Chong A, et al. Return to work and lost earnings after acute respiratory distress syndrome: a 5-year prospective, longitudinal study of long-term survivors. *Thorax*. 2018;73(2):125-133. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28918401>.
43. Azoulay E, Pochard F, Kentish-Barnes N, et al. Risk of post-traumatic stress symptoms in family members of intensive care unit patients. *Am J Respir Crit Care Med*. 2005;171(9):987-994. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15665319>.
44. Carfi A, Bernabei R, Landi F, Gemelli Against COVID-19 Post-Acute Care Study Group. Persistent symptoms in patients after acute COVID-19. *JAMA*. 2020;324(6):603-605. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32644129>.

Infection Control

Last Updated: October 9, 2020

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.

References

1. Yam LY, Chen RC, Zhong NS. SARS: ventilatory and intensive care. *Respirology*. 2003;8 Suppl:S31-35. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15018131>.
2. Twu SJ, Chen TJ, Chen CJ, et al. Control measures for severe acute respiratory syndrome (SARS) in Taiwan. *Emerg Infect Dis*. 2003;9(6):718-720. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/12781013>.
3. Centers for Disease Control and Prevention. The National Personal Protective Technology Laboratory (NPPTL): respirator trusted-source information. 2020. Available at: https://www.cdc.gov/niosh/npptl/topics/respirators/disp_part/respsource1quest2.html. Accessed September 23, 2020.
4. Milton DK, Fabian MP, Cowling BJ, Grantham ML, McDevitt JJ. Influenza virus aerosols in human exhaled breath: particle size, culturability, and effect of surgical masks. *PLoS Pathog*. 2013;9(3):e1003205. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23505369>.
5. Qian H, Li Y, Sun H, Nielsen PV, Huang X, Zheng X. Particle removal efficiency of the portable HEPA air cleaner in a simulated hospital ward. *Building Simulation*. 2010;3:215-224. Available at: <https://link.springer.com/article/10.1007/s12273-010-0005-4>.
6. Offeddu V, Yung CF, Low MSF, Tam CC. Effectiveness of masks and respirators against respiratory infections in healthcare workers: a systematic review and meta-analysis. *Clin Infect Dis*. 2017;65(11):1934-1942. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29140516>.

7. World Health Organization. Infection prevention and control during health care when novel coronavirus (nCoV) infection is suspected. 2020. Available at: [https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-\(ncov\)-infection-is-suspected-20200125](https://www.who.int/publications-detail/infection-prevention-and-control-during-health-care-when-novel-coronavirus-(ncov)-infection-is-suspected-20200125). Accessed April 8, 2020.
8. Centers for Disease Control and Prevention. Interim infection prevention and control recommendations for patients with suspected or confirmed coronavirus disease 2019 (COVID-19) in healthcare settings. 2020. Available at: <https://www.cdc.gov/coronavirus/2019-ncov/infection-control/control-recommendations.html>. Accessed September 28, 2020.
9. Bartoszko JJ, Farooqi MAM, Alhazzani W, Loeb M. Medical masks vs N95 respirators for preventing COVID-19 in healthcare workers: a systematic review and meta-analysis of randomized trials. *Influenza Other Respir Viruses*. 2020;14(4):365-373. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32246890>.
10. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22563403>.
11. Lewis SR, Butler AR, Parker J, Cook TM, Schofield-Robinson OJ, Smith AF. Videolaryngoscopy versus direct laryngoscopy for adult patients requiring tracheal intubation: a Cochrane Systematic Review. *Br J Anaesth*. 2017;119(3):369-383. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28969318>.

Laboratory Diagnosis

Last Updated: April 21, 2020

Recommendations:

- For intubated and mechanically ventilated adults who are suspected to have COVID-19 but who do not have a confirmed diagnosis:
 - The COVID-19 Treatment Guidelines Panel (the Panel) recommends obtaining lower respiratory tract samples to establish a diagnosis of COVID-19 over upper respiratory tract (nasopharyngeal or oropharyngeal) samples (**BII**).
 - The Panel recommends obtaining endotracheal aspirates over bronchial wash or bronchoalveolar lavage (BAL) samples when obtaining lower respiratory samples to establish a diagnosis of COVID-19 (**BII**).

Rationale

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) poses several diagnostic challenges, including potentially discordant shedding of virus from the upper versus lower respiratory tract. COVID-19 diagnosis is currently based on using a reverse transcriptase polymerase chain reaction (RT-PCR) assay to detect viral RNA in respiratory samples. The high specificity of RT-PCR removes the need for lower respiratory tract samples to diagnose COVID-19 when a nasopharyngeal swab is positive for a patient with recent onset of the disease. Lower respiratory tract specimens are considered by some experts to have higher yield, due to high viral load, consistent with what has been observed for severe acute respiratory syndrome (SARS) and Middle East respiratory syndrome (MERS).¹⁻⁷ Thus, lower respiratory tract samples should be obtained whenever possible if there is diagnostic uncertainty regarding COVID-19.

However, BAL and sputum induction are aerosol-generating procedures and should be performed only with careful consideration of the risk to staff of aerosol generation. Endotracheal aspirates appear to carry a lower risk of aerosolization than BAL and are thought by some experts to have comparable sensitivity and specificity to BAL specimens.

References

1. Chan PK, To WK, Ng KC, et al. Laboratory diagnosis of SARS. *Emerg Infect Dis*. 2004;10(5):825-831. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/15200815>.
2. Wang W, Xu Y, Gao R, et al. Detection of SARS-CoV-2 in different types of clinical specimens. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32159775>.
3. Centers for Disease Control and Prevention. Evaluating and testing persons for coronavirus disease 2019 (COVID-19). 2020; <https://www.cdc.gov/coronavirus/2019-nCoV/hcp/clinical-criteria.html>. Accessed April 8, 2020.
4. Hase R, Kurita T, Muranaka E, Sasazawa H, Mito H, Yano Y. A case of imported COVID-19 diagnosed by PCR-positive lower respiratory specimen but with PCR-negative throat swabs. *Infect Dis (Lond)*. 2020:1-4. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32238024>.
5. Tang P, Louie M, Richardson SE, et al. Interpretation of diagnostic laboratory tests for severe acute respiratory syndrome: the Toronto experience. *CMAJ*. 2004;170(1):47-54. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/14707219>.
6. Memish ZA, Al-Tawfiq JA, Makhdoom HQ, et al. Respiratory tract samples, viral load, and genome fraction yield in patients with Middle East respiratory syndrome. *J Infect Dis*. 2014;210(10):1590-1594. Available at:

<https://www.ncbi.nlm.nih.gov/pubmed/24837403>.

7. Centers for Disease Control and Prevention. Interim guidelines for collecting, handling, and testing clinical specimens from persons under investigation (PUIs) for Middle East respiratory syndrome coronavirus (MERS-CoV). Version 2.1. 2020. Available at: <https://www.cdc.gov/coronavirus/mers/guidelines-clinical-specimens.html>. Accessed April 8, 2020.

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.

References

1. Rhodes A, Evans LE, Alhazzani W, et al. Surviving Sepsis Campaign: international guidelines for management of sepsis and septic shock: 2016. *Crit Care Med*. 2017;45(3):486-552. Available at: <https://www.covid19treatmentguidelines.nih.gov/>

[ncbi.nlm.nih.gov/pubmed/28098591](https://www.ncbi.nlm.nih.gov/pubmed/28098591).

2. Bednarczyk JM, Fridfinnson JA, Kumar A, et al. Incorporating dynamic assessment of fluid responsiveness into goal-directed therapy: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(9):1538-1545. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28817481>.
3. Bentzer P, Griesdale DE, Boyd J, MacLean K, Sirounis D, Ayas NT. Will this hemodynamically unstable patient respond to a bolus of intravenous fluids? *JAMA*. 2016;316(12):1298-1309. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/27673307>.
4. Pan J, Peng M, Liao C, Hu X, Wang A, Li X. Relative efficacy and safety of early lactate clearance-guided therapy resuscitation in patients with sepsis: a meta-analysis. *Medicine (Baltimore)*. 2019;98(8):e14453. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30813144>.
5. Semler MW, Self WH, Wanderer JP, et al. Balanced crystalloids versus saline in critically ill adults. *N Engl J Med*. 2018;378(9):829-839. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29485925>.
6. Brown RM, Wang L, Coston TD, et al. Balanced crystalloids versus saline in sepsis. A secondary analysis of the SMART clinical trial. *Am J Respir Crit Care Med*. 2019;200(12):1487-1495. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31454263>.
7. Antequera Martin AM, Barea Mendoza JA, Muriel A, et al. Buffered solutions versus 0.9% saline for resuscitation in critically ill adults and children. *Cochrane Database Syst Rev*. 2019;7:CD012247. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31334842>.
8. Lewis SR, Pritchard MW, Evans DJ, et al. Colloids versus crystalloids for fluid resuscitation in critically ill people. *Cochrane Database Syst Rev*. 2018;8:CD000567. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30073665>.
9. Delaney AP, Dan A, McCaffrey J, Finfer S. The role of albumin as a resuscitation fluid for patients with sepsis: a systematic review and meta-analysis. *Crit Care Med*. 2011;39(2):386-391. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/21248514>.

Oxygenation and Ventilation

Last Updated: July 17, 2020

For hypoxemic patients, the recommendations below emphasize well-described and documented recommendations from the Surviving Sepsis Campaign Guidelines for [adult sepsis](#), [pediatric sepsis](#), and [COVID-19](#), which provide more details about management and the data that support the recommendations.

Recommendations

- For adults with COVID-19 who are receiving supplemental oxygen, the COVID-19 Treatment Guidelines Panel (the Panel) recommends close monitoring for worsening respiratory status and that intubation, if it becomes necessary, be performed by an experienced practitioner in a controlled setting (**AII**).
- 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 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 require intubation and mechanical ventilation (**AIII**).

Rationale

Hypoxemia is common in hospitalized patients with COVID-19. The criteria for hospital admission, intensive care unit (ICU) admission, and mechanical ventilation differ between countries. In some hospitals in the United States, >25% of hospitalized patients require ICU care, mostly due to acute respiratory failure.¹⁻⁵

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 include HFNC, NIPPV, or intubation and invasive mechanical ventilation.

HFNC and NIPPV are preferable to conventional oxygen therapy based on data from non-COVID-19 clinical trials and meta-analyses that showed reductions in the need for therapeutic escalation and the need for intubation in patients who received HFNC or NIPPV.^{6,7}

HFNC is preferred over NIPPV in patients with acute hypoxemic respiratory failure based on data from an unblinded clinical trial that was performed prior to the COVID-19 pandemic. This trial found more ventilator-free days with HFNC than with conventional oxygen therapy or NIPPV (24 days vs. 22 days vs. 19 days, respectively; $P = 0.02$) and lower 90-day mortality with HFNC than with either conventional oxygen therapy (hazard ratio [HR] 2.01; 95% confidence interval [CI], 1.01–3.99) or NIPPV (HR 2.50; 95% CI, 1.31–4.78).⁸

In the subgroup of more severely hypoxemic patients with $\text{PaO}_2/\text{FiO}_2 \leq 200$, HFNC reduced the rate

of intubation compared to conventional oxygen therapy or NIPPV (HRs 2.07 and 2.57, respectively). These findings were corroborated in a meta-analysis that showed a lower likelihood of intubation (odds ratio [OR] 0.48; 95% CI, 0.31–0.73) and ICU mortality (OR 0.36; 95% CI, 0.20–0.63) with HFNC than with NIPPV.⁹ In situations where the options for respiratory support are limited, reducing the need for intubation may be particularly important.

Prone positioning improves oxygenation and patient outcomes in patients with moderate-to-severe acute respiratory distress syndrome (ARDS) that requires mechanical ventilation.^{10,11} Prone positioning is thought to improve oxygenation because it improves ventilation-perfusion matching and recruits collapsed alveoli in the dorsal lungs.¹² Two case series that were published prior to the COVID-19 pandemic reported improved oxygenation and low intubation rates after placing spontaneously breathing patients with hypoxemia in the prone position,^{13,14} and several new case series reported similar results with awake prone positioning in patients with COVID-19 pneumonia who required supplemental oxygen.

In a case series of 50 patients with COVID-19 pneumonia who required supplemental oxygen upon presentation to a New York City emergency department (ED), awake prone positioning improved overall median oxygen saturation. However, 13 of these patients still required intubation due to respiratory failure within 24 hours of presentation to the ED.¹⁵ Another case series from Jiangsu province used awake prone positioning as part of a treatment strategy in nonintubated patients with COVID-19 pneumonia and reported an intubation rate of less than 1%.¹⁶ In a report of 24 patients who required either a nasal cannula or HFNC and who had a chest computed tomography scan that was consistent with COVID-19 pneumonia, 25% of patients tolerated prone positioning for at least 3 hours and showed >20% improvement in the partial pressure of oxygen in arterial blood. No complications were reported with prone positioning.¹⁷ Another case series of 15 patients with ARDS due to COVID-19 pneumonia who received awake prone positioning while on noninvasive ventilation reported that all patients showed improvement in their oxygen saturation during prone positioning, with 80% of patients maintaining their improved oxygen saturation after resupination. Seven percent of patients required intubation.¹⁸

Appropriate candidates for awake prone positioning are those who are able to 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 hemodynamically unstable patients, patients who recently had abdominal surgery, and patients who have an unstable spine.¹⁹ 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.²⁰

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

Early intubation may be particularly appropriate when patients have additional acute organ dysfunction or chronic comorbidities, or when HFNC and NIPPV are not available. NIPPV has a high failure rate in both patients with non-COVID-19 viral pneumonia^{21,22} and patients with ARDS.^{23,24} NIPPV may generate aerosol spread of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) and thus increase nosocomial transmission of the infection.^{25,26} It remains unclear whether HFNC results in a lower risk of nosocomial SARS-CoV-2 transmission.

The use of supplemental oxygen in adults with COVID-19 has not been studied, but indirect evidence from other critical illnesses suggests the optimal oxygen target is an SpO₂ between 92% and 96%:

- A meta-analysis of 25 randomized controlled trials found that a liberal oxygen strategy (median SpO₂ 96%) was associated with an increased risk of hospital mortality (relative risk 1.21; 95% CI, 1.03–1.43).²⁷

- The LOCO2 randomized controlled trial compared a conservative oxygen strategy (target SpO₂ 88% to 92%) to a liberal oxygen strategy (target SpO₂ ≥96%).²⁸ The trial was stopped early due to futility. Mortality increased among those who received the conservative oxygen therapy at Day 28 (risk difference +8%; 95% CI, -5% to +21%) and Day 90 (risk difference +14%; 95% CI, +0.7% to +27%). These differences would be important if they were real, but the study was too small to definitively confirm or exclude an effect.

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 tidal volumes (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

Currently, there is no evidence that ventilator management of patients with ARDS due to COVID-19 should differ from the management of patients with viral pneumonia due to influenza or other respiratory viruses.

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, 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 found lower rates of ICU mortality and in-hospital mortality with higher PEEP in patients with moderate (P/F ratio of 100–200) and severe ARDS (P/F ratio <100).²⁹

Though there is no clear standard as to what constitutes a high level PEEP, one conventional threshold is >10 cm H₂O.³⁰ Recent reports have suggested that, in contrast to other causes of ARDS, some patients with moderate or severe ARDS due to COVID-19 have normal static compliance; higher PEEP levels may cause harm in this group by compromising hemodynamics and cardiovascular performance.^{31,32} However, this finding has not been confirmed in other studies. Several observational 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.³³⁻³⁶ In patients with ARDS due to COVID-19, assessment for responsiveness to higher PEEP may be individualized based on oxygenation and lung compliance. Clinicians should monitor patients for known side effects of higher PEEP, such as barotrauma and hypotension.

Recommendations

- 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, which places the patient at risk for ventilator-induced lung injury, 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 more frequently for close clinical monitoring. Therefore, in some situations, the risks of COVID-19 exposure and the use of personal protective equipment for each entry may outweigh the benefit of NMBA treatment.

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**).

References

1. Guan WJ, Ni ZY, Hu Y, et al. Clinical characteristics of coronavirus disease 2019 in China. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32109013>.
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72,314 cases from the Chinese Center for Disease Control and Prevention. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32091533>.
3. Arentz M, Yim E, Klaff L, et al. Characteristics and outcomes of 21 critically ill patients with COVID-19 in Washington State. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32191259>.
4. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: guidelines on the management of critically ill adults with coronavirus disease 2019 (COVID-19). *Crit Care Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
5. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32031570>.
6. Xu XP, Zhang XC, Hu SL, et al. Noninvasive ventilation in acute hypoxemic nonhypercapnic respiratory failure: a systematic review and meta-analysis. *Crit Care Med*. 2017;45(7):e727-e733. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28441237>.
7. Zhao H, Wang H, Sun F, Lyu S, An Y. High-flow nasal cannula oxygen therapy is superior to conventional oxygen therapy but not to noninvasive mechanical ventilation on intubation rate: a systematic review and meta-analysis. *Crit Care*. 2017;21(1):184. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28701227>.

8. Frat JP, Thille AW, Mercat A, et al. High-flow oxygen through nasal cannula in acute hypoxemic respiratory failure. *N Engl J Med*. 2015;372(23):2185-2196. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25981908>.
9. Ni YN, Luo J, Yu H, Liu D, Liang BM, Liang ZA. The effect of high-flow nasal cannula in reducing the mortality and the rate of endotracheal intubation when used before mechanical ventilation compared with conventional oxygen therapy and noninvasive positive pressure ventilation. A systematic review and meta-analysis. *Am J Emerg Med*. 2018;36(2):226-233. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28780231>.
10. Guerin C, Reignier J, Richard JC, et al. Prone positioning in severe acute respiratory distress syndrome. *N Engl J Med*. 2013;368(23):2159-2168. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23688302>.
11. Fan E, Del Sorbo L, Goligher EC, et al. An official American Thoracic Society/European Society of Intensive Care Medicine/Society of Critical Care Medicine clinical practice guideline: mechanical ventilation in adult patients with acute respiratory distress syndrome. *Am J Respir Crit Care Med*. 2017;195(9):1253-1263. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/28459336>.
12. Nyren S, Mure M, Jacobsson H, Larsson SA, Lindahl SG. Pulmonary perfusion is more uniform in the prone than in the supine position: scintigraphy in healthy humans. *J Appl Physiol* (1985). 1999;86(4):1135-1141. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/10194194>.
13. Scaravilli V, Grasselli G, Castagna L, et al. Prone positioning improves oxygenation in spontaneously breathing nonintubated patients with hypoxemic acute respiratory failure: A retrospective study. *J Crit Care*. 2015;30(6):1390-1394. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/26271685>.
14. Ding L, Wang L, Ma W, He H. Efficacy and safety of early prone positioning combined with HFNC or NIV in moderate to severe ARDS: a multi-center prospective cohort study. *Crit Care*. 2020;24(1):28. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32000806>.
15. Caputo ND, Strayer RJ, Levitan R. Early self-proning in awake, non-intubated patients in the emergency department: a single ED's experience during the COVID-19 pandemic. *Acad Emerg Med*. 2020;27(5):375-378. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320506>.
16. Sun Q, Qiu H, Huang M, Yang Y. Lower mortality of COVID-19 by early recognition and intervention: experience from Jiangsu Province. *Ann Intensive Care*. 2020;10(1):33. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32189136>.
17. Elharrar X, Trigui Y, Dols AM, et al. Use of prone positioning in nonintubated patients with COVID-19 and hypoxemic acute respiratory failure. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32412581>.
18. Sartini C, Tresoldi M, Scarpellini P, et al. Respiratory parameters in patients with COVID-19 after using noninvasive ventilation in the prone position outside the intensive care unit. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32412606>.
19. Bamford P, Bentley A, Dean J, Whitmore D, Wilson-Baig N. ICS guidance for prone positioning of the conscious COVID patient. *Intensive Care Society*. 2020. Available at: <https://emcrit.org/wp-content/uploads/2020/04/2020-04-12-Guidance-for-conscious-proning.pdf>. Accessed May 14, 2020.
20. Society for Maternal Fetal Medicine. Management Considerations for Pregnant Patients With COVID-19. 2020. Available at: https://s3.amazonaws.com/cdn.smfm.org/media/2336/SMFM_COVID_Management_of_COVID_pos_preg_patients_4-30-20_final.pdf. Accessed: May 20, 2020.
21. Alraddadi BM, Qushmaq I, Al-Hameed FM, et al. Noninvasive ventilation in critically ill patients with the Middle East respiratory syndrome. *Influenza Other Respir Viruses*. 2019;13(4):382-390. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30884185>.
22. Esquinas AM, Egbert Pravinkumar S, Scala R, et al. Noninvasive mechanical ventilation in high-risk pulmonary infections: a clinical review. *Eur Respir Rev*. 2014;23(134):427-438. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/25445941>.

23. He H, Sun B, Liang L, et al. A multicenter RCT of noninvasive ventilation in pneumonia-induced early mild acute respiratory distress syndrome. *Crit Care*. 2019;23(1):300. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/31484582>.
24. Antonelli M, Conti G, Moro ML, et al. Predictors of failure of noninvasive positive pressure ventilation in patients with acute hypoxemic respiratory failure: a multi-center study. *Intensive Care Med*. 2001;27(11):1718-1728. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/11810114>.
25. Tran K, Cimon K, Severn M, Pessoa-Silva CL, Conly J. Aerosol generating procedures and risk of transmission of acute respiratory infections to healthcare workers: a systematic review. *PLoS One*. 2012;7(4):e35797. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/22563403>.
26. Yu IT, Xie ZH, Tsoi KK, et al. Why did outbreaks of severe acute respiratory syndrome occur in some hospital wards but not in others? *Clin Infect Dis*. 2007;44(8):1017-1025. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/17366443>.
27. Chu DK, Kim LH, Young PJ, et al. Mortality and morbidity in acutely ill adults treated with liberal versus conservative oxygen therapy (IOTA): a systematic review and meta-analysis. *Lancet*. 2018;391(10131):1693-1705. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29726345>.
28. Barrot L, Asfar P, Mauny F, et al. Liberal or conservative oxygen therapy for acute respiratory distress syndrome. *N Engl J Med*. 2020;382(11):999-1008. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32160661>.
29. Briel M, Meade M, Mercat A, et al. Higher vs lower positive end-expiratory pressure in patients with acute lung injury and acute respiratory distress syndrome: systematic review and meta-analysis. *JAMA*. 2010;303(9):865-873. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/20197533>.
30. Alhazzani W, Moller MH, Arabi YM, et al. Surviving Sepsis Campaign: Guidelines on the Management of Critically Ill Adults with Coronavirus Disease 2019 (COVID-19). *Crit Care Med*. 2020;48(6):e440-e469. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32224769>.
31. Marini JJ, Gattinoni L. Management of COVID-19 Respiratory Distress. *JAMA*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32329799>.
32. Tsolaki V, Siempos I, Magira E, Kokkoris S, Zakyntinos GE, Zakyntinos S. PEEP levels in COVID-19 pneumonia. *Crit Care*. 2020;24(1):303. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32505186>.
33. Bhatraju PK, Ghassemieh BJ, Nichols M, et al. Covid-19 in Critically Ill Patients in the Seattle Region - Case Series. *N Engl J Med*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32227758>.
34. Cummings MJ, Baldwin MR, Abrams D, et al. Epidemiology, clinical course, and outcomes of critically ill adults with COVID-19 in New York City: a prospective cohort study. *Lancet*. 2020;395(10239):1763-1770. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32442528>.
35. Ziehr DR, Alladina J, Petri CR, et al. Respiratory Pathophysiology of Mechanically Ventilated Patients with COVID-19: A Cohort Study. *Am J Respir Crit Care Med*. 2020;201(12):1560-1564. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32348678>.
36. Schenck EJ, Hoffman K, Goyal P, et al. Respiratory Mechanics and Gas Exchange in COVID-19 Associated Respiratory Failure. *Ann Am Thorac Soc*. 2020. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32432896>.

Acute Kidney Injury and Renal Replacement Therapy

Last Updated: June 11, 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. 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.

References

1. Richardson S, Hirsch JS, Narasimhan M, et al. Presenting characteristics, comorbidities, and outcomes among 5,700 patients hospitalized with COVID-19 in the New York City area. *JAMA*. 2020;323(20):2052-2059. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/32320003>.
2. American Society of Nephrology. Recommendations on the care of hospitalized patients with COVID-19 and kidney failure requiring renal replacement therapy. March 21, 2020. Available at: https://www.asn-online.org/g/blast/files/AKI_COVID-19_Recommendations_Document_03.21.2020.pdf.

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: April 21, 2020

Recommendation:

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

Rationale

While ECMO may serve as an effective short-term rescue therapy in patients with severe acute respiratory distress syndrome and refractory hypoxemia, there is no conclusive evidence that ECMO is responsible for better clinical outcomes in patients who received ECMO than in patients who did not receive ECMO.¹⁻⁴

ECMO is used by some experts, when available, for patients with refractory hypoxemia despite optimization of ventilation strategies and adjunctive therapies. Ideally, clinicians who are interested in using ECMO should either try to enter their patient 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:

- [Extracorporeal Life Support Organization](#)
- [Clinical trials evaluating ECMO in patients with COVID-19](#) on [ClinicalTrials.gov](#).

References

1. Peek GJ, Mugford M, Tiruvoipati R, et al. Efficacy and economic assessment of conventional ventilatory support versus extracorporeal membrane oxygenation for severe adult respiratory failure (CESAR): a multicentre randomised controlled trial. *Lancet*. 2009;374(9698):1351-1363. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/19762075>.
2. Pham T, Combes A, Roze H, et al. Extracorporeal membrane oxygenation for pandemic influenza A(H1N1)-induced acute respiratory distress syndrome: a cohort study and propensity-matched analysis. *Am J Respir Crit Care Med*. 2013;187(3):276-285. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/23155145>.
3. Harrington D, Drazen JM. Learning from a trial stopped by a data and safety monitoring board. *N Engl J Med*. 2018;378(21):2031-2032. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/29791830>.
4. Munshi L, Walkey A, Goligher E, Pham T, Uleryk EM, Fan E. Venovenous extracorporeal membrane oxygenation for acute respiratory distress syndrome: a systematic review and meta-analysis. *Lancet Respir Med*. 2019;7(2):163-172. Available at: <https://www.ncbi.nlm.nih.gov/pubmed/30642776>.