Managing Critically Ill Patients with COVID-19

About the Guideline

- This guideline provides recommendations to support hospital clinicians managing critically ill adults with COVID-19 in the ICU.
- The target users of this guideline are frontline clinicians, allied health professionals, and policymakers involved in the care of patients with COVID-19 in the ICU.
- A panel of 36 experts from 12 countries reviewed the literature and identified relevant and recent evidence on supportive care for COVID-19 patient in the intensive care unit (ICU).
- Recommendations were generated based on the balance between benefit and harm, resource and cost implications, equity, and feasibility.

Overview

- Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is the cause of a rapidly spreading illness, Coronavirus Disease 2019 (COVID-19).
- Recommendations are organized based on five topics:
  1. Infection control
  2. Laboratory diagnosis and specimens
  3. Hemodynamic support
  4. Ventilatory support
  5. COVID-19 therapy

Key Clinical Considerations

Infection control

- Current data points to significant burden of infection among healthcare workers.
- Risk of patient-to-patient transmission in the ICU is currently unknown.
- Adherence to infection control precautions is paramount.
- Infection control policies and procedures already in place at healthcare institutions should be followed; the recommendations in this guideline should serve as considerations rather than a requirement to change policies.

Aerosol-generating procedures

- **Best Practice Statement:** For healthcare workers performing aerosol-generating procedures on patients with COVID-19 in the ICU, the recommendation is to use fitted respirator masks (N95 respirators, FFP2, or equivalent), as opposed to surgical/medical masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles).
- Aerosol-generating procedures include:
  - endotracheal intubation
  - bronchoscopy
Use of negative pressure rooms
- **Best Practice Statement:** The *recommendation* is to perform aerosol-generating procedures on ICU patients with COVID-19 in a negative pressure room.
- Negative pressure rooms are intended to prevent the spread of contagious airborne pathogens from room to room and avoid the accidental release of pathogens into a larger space and open facility.
- When not feasible, a portable high-efficiency particulate air (HEPA) filter should be used.
- The presence of unnecessary staff in the room should be avoided.

Usual care of nonventilated patients
- Weak recommendation, low quality evidence: For healthcare workers providing usual care for non-ventilated COVID-19 patients, the *suggestion* is to use surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles).

Non-aerosol-generating procedures on ventilated (closed-circuit) patients
- Weak recommendation, low quality evidence: For healthcare workers who are performing non-aerosol-generating procedures on mechanically ventilated (closed circuit) patients with COVID-19, the *suggestion* is to use surgical/medical masks, as opposed to respirator masks, in addition to other personal protective equipment (i.e., gloves, gown, and eye protection, such as a face shield or safety goggles).

Endotracheal intubation
- Techniques that can reduce the number of attempts at endotracheal intubation and the duration of the procedure and minimize the proximity between the operator and the patient should be prioritized.
- **Best Practice Statement:** For COVID-19 patients requiring endotracheal intubation, the *recommendation* is that endotracheal intubation be performed by the healthcare worker who is most experienced with airway management in order to minimize the number of attempts and risk of transmission.
- Weak recommendation, low quality evidence: For healthcare workers performing endotracheal intubation on patients with COVID-19, the *suggestion* is to use video-guided laryngoscopy, over direct laryngoscopy, if available.
Laboratory diagnosis and specimens

- Every critically ill patient arriving with evidence of respiratory infection should be considered potentially infected with SARS-CoV-2.
- Diagnostic challenges exist due to an extended incubation period (approximately two weeks) that includes a prolonged interval (approximately five days) of viral shedding prior to the onset of symptoms.
- The duration of asymptomatic shedding varies and may also differ based on the anatomic level (upper versus lower) of the infection in the respiratory system.
- A single negative swab from the upper airway does not rule out SARS-CoV-2 infection; repeated sampling from multiple sites, including the lower airway, will increase diagnostic yield.
- A positive test for another respiratory virus does not rule out COVID-19 and should not delay testing if there is a high suspicion of COVID-19.
- A single positive swab confirms the diagnosis of COVID-19.

Intubated and mechanically ventilated adults with suspicion of COVID-19

- Weak recommendation, low quality evidence: For diagnostic testing, the *suggestion* is to obtain lower respiratory tract samples in preference to upper respiratory tract (nasopharyngeal or oropharyngeal).
- Weak recommendation, low quality evidence: Regarding lower respiratory samples, the *suggestion* is to obtain endotracheal aspirates in preference to bronchial wash or bronchoalveolar lavage samples.

Hemodynamic support

- The incidence of shock in adult patients with COVID-19 may reach 20-35% among patients in the ICU.

Fluid therapy

- Weak recommendation, low quality evidence: In adults with COVID-19 and shock, the *suggestion* is to use dynamic parameters, skin temperature, capillary refilling time, and/or serum lactate measurement over static parameters in order to assess fluid responsiveness.
  - This recommendation is based on indirect evidence drawn from critically ill patients in general.
    - Dynamic parameters include stroke volume variation, pulse pressure variation, and stroke volume change with passive leg raise or fluid challenge.
    - Static parameters include central venous pressure and mean arterial pressure (MAP).
- Weak recommendation, low quality evidence: For the acute resuscitation of adults with COVID-19, the *suggestion* is to use a conservative over a liberal fluid strategy.
  - This suggestion is based on indirect evidence drawn from critically ill patients with sepsis and acute respiratory distress syndrome (ARDS).
- Strong recommendation, moderate quality evidence: For the acute resuscitation of adults with COVID-19 and shock, the *recommendation* is to use crystalloids over colloids.
- This recommendation is based on indirect evidence drawn from critically ill patients in general.

- **Weak recommendation, moderate quality evidence:** For the acute resuscitation of adults with COVID-19 and shock, the *suggestion* is to use buffered/balanced crystalloids over unbalanced crystalloids.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.
  - In settings with limited availability of buffered solutions, 0.9% saline is a reasonable alternative.

- **Strong recommendation, moderate quality evidence:** For the acute resuscitation of adults with COVID-19 and shock, the *recommendation* is against using hydroxyethyl starches.
  - This recommendation is based on indirect evidence drawn from critically ill patients in general.

- **Weak recommendation, low quality evidence:** For the acute resuscitation of adults with COVID-19 and shock, the *suggestion* is against using gelatins.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.

- **Weak recommendation, low quality evidence:** For the acute resuscitation of adults with COVID-19 and shock, the *suggestion* is against using dextrans.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.

- **Weak recommendation, moderate quality evidence:** For the acute resuscitation of adults with COVID-19 and shock, the *suggestion* is against the routine use of albumin for initial resuscitation.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.

**Vasoactive agents**

- **Weak recommendation, low quality evidence:** For adults with COVID-19 and shock, the *suggestion* is to use norepinephrine as the first line vasoactive agent, over other agents.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.

- **Weak recommendation, low quality evidence:** If norepinephrine is not available, the *suggestion* is to use either vasopressin or epinephrine as the first line vasoactive agent, over other vasoactive agents for adults with COVID-19 and shock.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.
  - The decision between vasopressin and epinephrine may be based on availability and contraindications to the two agents.
    - With vasopressin, digital ischemia may be a concern.
    - With epinephrine, tachycardia and excess lactate production may be concerns.

- **Strong recommendation, high quality evidence:** For adults with COVID-19 and shock, the *recommendation* is against using dopamine if norepinephrine is available.
  - This recommendation is based on indirect evidence drawn from critically ill patients in general.
  - This recommendation is based on increased harm, including increased risk of mortality, in patients treated with dopamine.
- Weak recommendation, moderate quality evidence: For adults with COVID-19 and shock, the *suggestion* is to add vasopressin as a second line agent, over titrating norepinephrine dose, if target MAP cannot be achieved by norepinephrine alone.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.
- Weak recommendation, low quality evidence: For adults with COVID-19 and shock, the *suggestion* is to titrate vasoactive agents to target a MAP of 60-65 mmHg, rather than higher MAP targets.
  - This suggestion is based on indirect evidence drawn from critically ill patients.
- Weak recommendation, very low quality evidence: For adults with COVID-19 and shock with evidence of cardiac dysfunction and persistent hypoperfusion despite fluid resuscitation and norepinephrine, the *suggestion* is to add dobutamine, over increasing norepinephrine dose.
  - This suggestion is based on indirect evidence drawn from critically ill patients.
  - It is also *suggested* to add dobutamine, over no treatment, in these patients; this is based on physiological rationale.
- Weak recommendation, low quality evidence: For adults with COVID-19 and refractory shock, the *suggestion* is to use low dose corticosteroid therapy (“shock reversal”), over no corticosteroid therapy.
  - This suggestion is based on indirect evidence drawn from critically ill patients in general.
  - A typical regimen in septic shock is intravenous hydrocortisone 200 mg per day administered as an infusion or intermittent doses.

**Ventilatory support**

- The true incidence of hypoxic respiratory failure in patients with COVID-19 is unclear, however about 14% will develop severe disease requiring oxygen therapy and 5% will require ICU admission and mechanical ventilation.
- In another study, 67% of critically ill COVID-19 patients had ARDS, 63.5% received high flow nasal cannula (HFNC), 56% required invasive mechanical ventilation, and 42% received non-invasive positive pressure ventilation (NIPPV).

**Oxygen therapy**

- A reasonable SPO₂ range for patients on oxygen therapy is 92% to 96%.
  - Weak recommendation, low quality evidence: In adults with COVID-19, the *suggestion* is to start supplemental oxygen if the peripheral oxygen saturation (SPO₂) is <92%.
  - Strong recommendation, moderate quality evidence: In adults with COVID-19, the *recommendation* is to start supplemental oxygen if the SPO₂ is <90%.
  - Strong recommendation, moderate quality evidence: In adults with COVID-19 and acute hypoxemic respiratory failure on oxygen, the *recommendation* is that SPO₂ be maintained no higher than 96%.
- Weak recommendation, low quality evidence: For adults with COVID-19 and acute hypoxemic respiratory failure despite conventional oxygen therapy, the *suggestion* is to use HFNC over conventional oxygen therapy.
  - This suggestion is based on indirect evidence from the critically ill population.
• Weak recommendation, low quality evidence: For adults with COVID-19 and acute hypoxemic respiratory failure, the suggestion is to use HFNC over NIPPV.
  o There is evidence for decreased risk of intubation with HFNC compared with NIPPV in acute respiratory failure.
  o Some studies suggest that NIPPV may carry a greater risk of nosocomial infection of healthcare providers.

• Weak recommendation, very low quality evidence: In adults with COVID-19 and acute hypoxemic respiratory failure, if HFNC is not available and there is no urgent indication for endotracheal intubation, the suggestion is a trial of NIPPV with close monitoring and short interval assessment for worsening of respiratory failure.

• Best Practice Statement: In adults with COVID-19 receiving NIPPV or HFNC, the recommendation is for close monitoring for worsening of respiratory status and early intubation in a controlled setting if worsening occurs.
  o Limited experience with NIPPV in pandemics suggests a high failure rate.
  o When resources become stretched, if there is insufficient ability to provide invasive ventilation, a moderate chance of success with NIPPV may justify its use.

Invasive mechanical ventilation
• Strong recommendation, moderate quality evidence: In mechanically ventilated adults with COVID-19 and ARDS, the recommendation is to use low tidal volume (Vt) ventilation (Vt 4-8 mL/kg of predicted body weight) over higher tidal volumes (Vt > 8 mL/kg).
  o The panel of experts believes that COVID-19 patients should be managed as others with acute respiratory failure in the ICU.
  o Low Vt ventilation is one of the main strategies to minimize ventilator-induced lung injury (VILI).
  o The ARDSNet study protocol set the initial Vt at 6 mL/kg which can be increased to 8 mL/kg if the patient is double triggering or if inspiratory airway pressure decreases below PEEP.

• Strong recommendation, moderate quality evidence: For mechanically ventilated adults with COVID-19 and ARDS, the recommendation is targeting plateau pressures (Pplat) of <30 cm H2O.
  o Pplat limitation is a lung protective strategy to minimize VILI.
  o The ARDSNet study protocol set the initial Vt at 6 mL/kg, and then measured Pplat (after a 0.5 second inspiratory pause). If the Pplat > 30 cmH2O, Vt could be reduced in 1 mL/kg (to 4 mL/kg) steps until Pplat was within range.

• Weak recommendation, low quality evidence: For mechanically ventilated adults with COVID-19, the suggestion is to use a higher PEEP strategy over a lower PEEP strategy.
  o PEEP increases and sustains alveolar recruitment, which improves oxygenation.
  o If using a higher PEEP strategy (i.e. PEEP > 10 cm H2O), monitor patients for barotrauma.

• Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and ARDS, the suggestion is to use a conservative fluid strategy over a liberal fluid strategy.
  o Limited data show that cardiac failure, alone or with respiratory failure, caused 40% of COVID-19 deaths.
• Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and moderate to severe ARDS, the **suggestion** is to use prone ventilation for 12 to 16 hours, over no prone ventilation.
  o The progression of radiographic features in a series of COVID-19 patients suggests a role for prone ventilation.
  o Theoretically, prone positioning decreases ventral alveolar distention and dorsal alveolar collapse.
  o A protocol for proning should be used.
  o Clinicians should be aware of the following complications:
    ▪ Pressure sores
    ▪ Vascular line and endotracheal tube displacement
    ▪ Facial edema
    ▪ Transient hemodynamic instability
    ▪ Corneal abrasions
    ▪ Brachial plexus injury
    ▪ Hemodialysis vascular flow issues
  o Absolute contraindications for prone ventilation are:
    ▪ Unstable spine
    ▪ Open abdomen or open chest
  o Enteral nutrition (via nasogastric or nasoduodenal tube) can be continued during proning.

• Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and moderate to severe ARDS, the **suggestion** is to use intermittent boluses of neuromuscular blocking agents (NMBA) as needed, over continuous NMBA infusion.

• Weak recommendation, low quality evidence: In the event of persistent ventilator dyssynchrony, the need for ongoing deep sedation, prone ventilation, or persistently high plateau pressures, for mechanically ventilated adult patients with COVID-19 and moderate to severe ARDS, the **suggestion** is to use a continuous NMBA infusion for up to 48 hours.

• Strong recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and moderate to severe ARDS, the **recommendation** is against routine use of inhaled nitric oxide.

• Weak recommendation, very low quality evidence: For mechanically ventilated adult patients with COVID-19, severe ARDS, and hypoxemia despite optimizing ventilation and other rescue strategies, the **suggestion** is a trial of inhaled pulmonary vasodilator as a rescue therapy; treatment should be tapered off if there is no rapid improvement in oxygenation.

• Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and hypoxemia despite optimizing ventilation, the **suggestion** is to use recruitment maneuvers (RM).
  o Strong recommendation, moderate quality evidence: If RM are used, the **recommendation** is against using staircase (incremental PEEP).
  o Examples of two traditional RMs:
    ▪ Prolonged inspiratory holds for a set duration of time on higher levels of CPAP (most commonly 35 to 40 cm H₂O for 40 seconds.)
 Incremental PEEP titration RM s are described as incremental increases in PEEP from 25 to 35 cm H₂O for 1-2 minutes each.
  o Monitor patients closely for severe desaturation, hypotension, or barotrauma.
  o Stop RM s if they lead to patient deterioration.

 Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and hypoxemia despite optimizing ventilation, use of rescue therapies, and proning, the suggestion is to use venovenous (VV) extracorporeal membrane oxygenation (ECMO) if available, or referring patient to an ECMO center.
  o ECMO is a resource intensive technique and remains a limited resource; its use should be reserved for carefully selected patients.

 COVID-19 therapy

 Cytokine storm syndrome is a hyperinflammatory state characterized by fulminant multi-organ failure and elevated cytokine levels. A recent study from China showed that COVID-19 is associated with a cytokine elevation profile similar to that of secondary hemophagocytic lymphohistiocytosis (HLH).

 Corticosteroids

 Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and respiratory failure (without ARDS), the suggestion is against routine use of systemic corticosteroids.

 Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and ARDS, the suggestion is to use systemic corticosteroids, over not using corticosteroids.

 Indirect evidence from community acquired pneumonia, ARDS, and other viral infections are the basis of these suggestions.

 If corticosteroids are used in ARDS patients, lower dosing and shorter treatment courses are advised.

 Antimicrobials

 Weak recommendation, low quality evidence: For mechanically ventilated adult patients with COVID-19 and respiratory failure, the suggestion is to use empiric antimicrobials/antibacterial agents, over no antimicrobials.
  o If used, assessment for de-escalation should be done daily, along with re-evaluation of duration of therapy and spectrum of coverage based on microbiology results and clinical status of patient.
  o This suggestion is based on extrapolation of data from other viral pneumonias, particularly influenza.

 Temperature control

 Weak recommendation, low quality evidence: For critically ill adult patients with COVID-19, the suggestion is to use acetaminophen/paracetamol for temperature control.
  o Increasing patient comfort through fever management may be important.
The use of non-steroidal anti-inflammatory drugs to treat fever in patients with COVID-19 continues to be debated.

**Immunoglobulins**
- Weak recommendation, very low quality evidence: In critically ill adults with COVID-19, the *suggestion* is against routine use of standard intravenous immunoglobulins (IVIG).
  - IVIG can cause serious adverse events including:
    - Anaphylactic reactions
    - Aseptic meningitis
    - Renal failure
    - Thromboembolism
    - Hemolytic reactions
    - Transfusion-related lung injury
    - Other late reactions
- Anti-SARS-CoV-2 polyclonal or monoclonal antibodies are being developed.

**Convalescent plasma**
- Weak recommendation, very low quality evidence: In critically ill adults with COVID-19, the *suggestion* is against routine use of convalescent plasma.
  - A lack of convincing evidence and uncertainty about optimal preparation of convalescent plasma and its safety are the basis of this suggestion.

**Antivirals**
- Weak recommendation, low quality evidence: In critically ill adults with COVID-19, the *suggestion* is against routine use of lopinavir/ritonavir.
  - There is insufficient evidence on use of other antiviral agents.

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

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

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

Reference:
Link to Practice Guideline: