

Clinical Management of Patients with Moderate to Severe COVID-19 - Interim Guidance

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This guidance document was prepared by: Dr. R. Fowler, Dr. T. Hatchette, Dr. M. Salvadori, Dr. M. Ofner, Dr. G. Poliquin, Dr. T. Yeung & Dr. J. Brooks on behalf of the COVID-19 Clinical Care Guidance Working Group. **Scientific Writer:** Dr. S. Tamblyn.

The guidance document has been endorsed by: Canadian Critical Care Society and Association of Medical Microbiology and Infectious Disease (AMMI) Canada.

COVID-19 Clinical Care Guidance Working Group members: Dr. R. Fowler (Co-chair), Dr. T. Hatchette (Co-chair), M-E Delvin, Dr. D. Kitty, Dr. J. Leis, Dr. D. Money, Dr. S. Murthy, Dr. M. Ofner, Dr. G. Poliquin, Dr. S. Tamblyn, Dr. M. Salvadori, P. St-Louis & Dr. T. Yeung.

Canadian Critical Care Society reviewers: Dr. K. Burns, Dr. F. D'Aragon, Dr. J. Downar, Dr. C. Farrell, Dr. B. Haroon & Dr. A. Fox-Robichaud.

Association of Medical Microbiology and Infectious Disease (AMMI) Canada reviewers:

Dr. G. Evans, Dr. S. Forgie, Dr. S. Hota, Dr. S. Mubareka, Dr. J. Papenburg.

Additional reviewers: Dr. G. Emeriaud, Dr. N. Adhikari, Dr. S. Funnel, Dr. T. Haffner, Dr. A. Kara, Dr. A. Kestler & Dr. T. Wong.

PHAC support : Y-E Chung, M. Kamkar, M. Kamanga & T. Wang.

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Preamble

This guidance has been adapted for Canadian use from the WHO document entitled *Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected – Interim guidance - 13 March 2020*. (Available from: <https://www.who.int/emergencies/diseases/novel-coronavirus-2019/technical-guidance/patient-management>). This guidance is informed by currently available scientific evidence and expert opinion, and is subject to change as new information becomes available.

This guidance provides clinicians with interim advice on timely, effective, and safe supportive management of adult and paediatric patients with suspected or confirmed COVID-19. It is not meant to replace clinical judgment or specialist consultation, but rather to strengthen the clinical management of these patients. Best practices for triage and optimized supportive care are included.

This guidance builds on evidence-informed guidelines developed by a multidisciplinary panel of health care providers with experience in the clinical management of patients with COVID-19 and other viral infections (including SARS and MERS) as well as sepsis and acute respiratory distress syndrome (ARDS) (5,6). It should serve as a foundation to optimize supportive care to ensure the best possible chance for survival and to allow reliable comparisons of investigational interventions as part of randomized controlled trials (RCTs).

In the guidelines, these symbols are used to flag interventions:

- ✔ Do – the intervention is beneficial (strong recommendation) **OR** the intervention is a best practice statement
- ✘ Don't – the intervention is known to be harmful.
- ! Consider – the intervention may be beneficial in selected patients (conditional recommendation) **OR** be careful when considering this intervention.

1.0 Background

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection caused by a newly emergent coronavirus that was first recognized in Wuhan, China in December 2019. Genetic sequencing of the virus suggests that it is a betacoronavirus closely linked to the SARS virus (1).

While most people with COVID-19 develop mild or uncomplicated illness, experience in China found that approximately 14% developed severe disease requiring hospitalization and oxygen support and 5% required admission to an intensive care unit (ICU) (1). In severe cases, COVID-19 can be complicated by ARDS; sepsis and septic shock; and multiorgan failure, including acute kidney injury and cardiac injury (2). Older age and co-morbid disease have been reported as risk factors for death, and recent multivariate analysis confirmed that older age and higher Sequential Organ Failure Assessment (SOFA) score on admission were associated with higher mortality.

There are few data on the clinical presentation of COVID-19 in specific populations, such as children and pregnant women. In children with COVID-19 the symptoms are usually less severe than adults and consist mainly of cough and temperature over 38°C (7,8). Relatively few infant COVID-19 cases have been reported; those experienced relatively mild illness (9). There is currently no known difference between the clinical

manifestations of COVID-19 infected pregnant or non-pregnant women of reproductive age; however, experience with severe viral respiratory illness from other etiologies emphasizes the need for unique appreciation of pregnancy-related critical illness.

2.0 Screening and Triage

✔ **Screening and Triage – Screen and isolate all patients with suspected COVID-19 at the first point of contact with the health care system (such as the emergency department or outpatient department/clinic). Consider COVID-19 as a possible etiology in patients presenting with acute respiratory illness. Triage patients using standardized triage tools and manage initial presentations accordingly.**

Remarks

- [National surveillance case definitions](#) have been developed to standardize public health reporting. These case definitions, however, are not to be used for clinical purposes.
- Early recognition of suspected patients allows for timely initiation of appropriate infection prevention and control measures (see [Section 3.0](#)). Table 1 below outlines the syndromes most often associated with COVID-19.
- Most people with COVID-19 have uncomplicated or mild illness (81%). Some will develop severe illness requiring oxygen therapy and approximately 5% will develop critical illness requiring intensive care unit (ICU) treatment. Of those critically ill, most will require mechanical ventilation (2,10).
- For those with mild illness, hospitalization is not required unless there is concern about rapid deterioration or inability to return promptly to hospital.
- Isolation is necessary to contain virus transmission. All patients cared for outside hospital (i.e., at home) should be instructed to follow public health protocols for self-isolation and return to hospital if they get worse.
- Early identification of those with severe illness or pneumonia, allows for optimized supportive care treatments and safe, rapid referral and admission to a hospital.
- Older patients and those with comorbidities (e.g. cardiovascular disease, diabetes mellitus, pre-existing lung conditions) have increased risk of severe disease and mortality. While they may present with mild disease, they have a higher risk of deterioration and should be monitored closely.
- Goals of care discussions should be a component of care for all patients, especially so, for patients with, or at risk of, severe disease. For patients who do not receive intensive and organ-supportive care in severe illness, symptom-based and palliative care should be offered as appropriate.

Table 1 – Clinical Syndromes Associated with COVID-19

Syndrome	Details
Mild illness	Patients with uncomplicated upper respiratory tract viral infection may have non-specific symptoms such as fever, fatigue, cough (with or without sputum production), anorexia, malaise, muscle pain, sore throat, dyspnea, nasal congestion, or headache. Patients may also present with diarrhea, abdominal pain, nausea and vomiting (3,11-13). Many are afebrile or have low-grade fever. The elderly and immunocompromised may present with atypical symptoms. Symptoms due to physiologic adaptations of pregnancy or adverse pregnancy events, e.g., dyspnea, fever, GI symptoms or fatigue, may overlap with COVID-19 symptoms.
Pneumonia	Adult with pneumonia but no signs of severe pneumonia and no need for supplemental oxygen.

Syndrome	Details
	Child with non-severe pneumonia who has cough or difficulty breathing plus tachypnea (in breaths per minute) : < 2 months: ≥ 60 ; 2–11 months: ≥ 50 ; 1–5 years: ≥ 40), and no signs of severe pneumonia.
Less common presentations	Both adults and children can present with nausea, vomiting, abdominal pain and/or diarrhea. This presentation is seen in about 5% of adults and is more common in children. Other non-specific or unusual presentations can also occur in the absence of initial respiratory symptoms.
Severe pneumonia	Adolescent or adult: fever or suspected respiratory infection, plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO ₂ < 93% on room air (adapted from ref 14). Child with cough and/or difficulty in breathing, plus at least one of the following: central cyanosis or SpO ₂ < 90%; severe respiratory distress (e.g. grunting, marked chest indrawing); signs of pneumonia with: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (15). Other signs of pneumonia may be present: fast breathing (in breaths/min) < 2 months: ≥ 60 ; 2–11 months: ≥ 50 ; 1–5 years: ≥ 40 (16). While the diagnosis can be made on clinical grounds, chest imaging may identify some pulmonary complications.
Acute respiratory distress syndrome (ARDS) (17-19)	Onset: within 1 week of a known clinical insult or new or worsening respiratory symptoms. Chest imaging (X-ray, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. Origin of pulmonary infiltrates: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/edema if no risk factor present. Oxygenation impairment in adults: (17,19) <ul style="list-style-type: none"> mild ARDS: $200 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2^a \leq 300 \text{ mmHg}$ (with PEEP or CPAP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) moderate ARDS: $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) severe ARDS: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ with PEEP $\geq 5 \text{ cmH}_2\text{O}$, or non-ventilated) when PaO₂ is not available, SpO₂/FiO₂ ≤ 315 suggests ARDS (including in non-ventilated patients) Oxygenation impairment in children: Note OI = Oxygenation Index and OSI = Oxygenation Index using SpO ₂ . Use PaO ₂ -based metric when available. If PaO ₂ not available, wean FiO ₂ to maintain SpO ₂ at 92-97% to calculate OSI or SpO ₂ /FiO ₂ ratio: <ul style="list-style-type: none"> bilevel NIV or CPAP $\geq 5 \text{ cmH}_2\text{O}$ via full face mask: $\text{PaO}_2/\text{FiO}_2 \leq 300 \text{ mmHg}$ or $\text{SpO}_2/\text{FiO}_2 \leq 264$ mild ARDS (invasively ventilated): $4 \leq \text{OI} < 8$ or $5 \leq \text{OSI} < 7.5$ moderate ARDS (invasively ventilated): $8 \leq \text{OI} < 16$ or $7.5 \leq \text{OSI} < 12.3$ severe ARDS (invasively ventilated): $\text{OI} \geq 16$ or $\text{OSI} \geq 12.3$
Sepsis (5,6)	Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. ^b Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output (5,20), fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate or hyperbilirubinemia. Children: suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome criteria, of which one must be abnormal temperature or white blood cell count for age.
Septic shock (5,6)	Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP $\geq 65 \text{ mmHg}$ and serum lactate level > 2 mmol/L. Children: any hypotension (SBP < 5th centile or > 2 SD below normal for age) or 2 or 3 of the following: altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; tachypnea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia (21). Children often have tachycardia before rapid onset of hypotension occurs.

Footnotes

a If altitude is higher than 1000m, then correction factor should be calculated as follows: $\text{PaO}_2/\text{FiO}_2 \times \text{barometric pressure}/760$.

b The SOFA score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxemia defined by low $\text{PaO}_2/\text{FiO}_2$); coagulation (low platelets); liver (high bilirubin); cardiovascular (hypotension); central nervous system (low level of consciousness defined by Glasgow Coma Scale); and renal (low urine output or high creatinine).

Sepsis is defined by an increase in the sepsis-related SOFA score of ≥ 2 points. Assume the baseline score is 0 if data are not available (21).

Abbreviations: ARI acute respiratory infection; BP blood pressure; bpm beats/minute; CPAP continuous positive airway pressure; FiO_2 fraction of inspired oxygen; MAP mean arterial pressure; NIV non-invasive ventilation; OI Oxygenation Index; OSI Oxygenation Index using SpO_2 ; PaO_2 partial pressure of oxygen; PEEP positive end-expiratory pressure; SBP systolic blood pressure; SD standard deviation; SIRS systemic inflammatory response syndrome; SOFA sequential organ failure assessment; SpO_2 oxygen saturation.

3.0 Infection Prevention and Control Measures

Infection prevention and control (IPC) is a critical and integral part of the clinical management of patients. Detailed national IPC guidance for COVID-19 in acute health care settings is available from the Public Health Agency of Canada (PHAC). See <https://www.canada.ca/en/public-health/services/diseases/2019-novel-coronavirus-infection/health-professionals.html>. Some provinces and territories have also issued IPC guidance for their jurisdiction.

IPC guidance documents are revised and updated as new evidence becomes available therefore refer to the guidance documents directly

4.0 Collection of Specimens for Laboratory Diagnosis

COVID-19 testing may be performed for surveillance and diagnostic reasons. Testing criteria recommendations are necessarily dynamic as the situation evolves in regions. All hospitalized patients who are clinically suspected of infection with COVID-19 should be tested.

Guidance on appropriate testing and specimen collection for COVID-19 is available from the Canadian Public Health Laboratory Network (<https://nccid.ca/cphln/?highlight=cphln#038;hilite=%27cphln%27>), and from provincial/territorial Public Health Laboratories. Testing may be prioritized to preserve limited resources.

✔ **Collect specimens for COVID-19 testing as recommended by your local or provincial public health laboratory.**

✔ **Collect blood cultures for bacteria that cause pneumonia and sepsis, ideally before antimicrobial therapy. DO NOT delay antimicrobial therapy to collect blood cultures. Blood cultures should be done in children if clinically indicated.**

Remarks

- In admitted patients with suspected COVID-19, the diagnosis should be first attempted with an upper respiratory specimen, preferably a nasopharyngeal swab. However, a nasal and/or throat swab can be collected as an alternative if nasopharyngeal swabs are not available. For admitted patients with suspected COVID-19, if the upper respiratory swab is negative and there remains a high degree of clinical suspicion a repeat swab should be collected. In severely ill patients whose upper respiratory tract

specimen is negative but a COVID-19 diagnosis is still suspected, a lower respiratory tract specimen consisting of sputum, or closed system suctioned endotracheal aspirate should also be collected when possible (e.g., if the patient is producing sputum or they are already ventilated). Once a patient has a positive laboratory test, further testing for diagnostic purposes is not necessary (23).

- Dual infections with other respiratory viral and bacterial infections have been found in COVID-19 patients. As a result, a positive test for a non-COVID-19 pathogen, such as another respiratory virus, does not rule out COVID-19 and vice versa.
- Serology for COVID-19 is not routinely available at this time.

5.0 Management of Mild COVID-19

- ✓ **Patients with mild disease do not require hospitalization, unless there is concern for rapid deterioration or an inability to return promptly to hospital.**
- ✓ **Isolation is necessary to contain virus transmission.** All patients cared for outside hospital should be instructed to follow public health protocols for self-isolation and return to hospital if symptoms worsen. Self-isolation protocols are available from PHAC and provincial/territorial and local public health departments.
- ✓ **Provide patients with mild COVID-19 information on symptomatic treatment.**
- ✓ **Counsel patients with mild COVID-19 about the signs and symptoms of worsening disease.** If they develop symptoms like difficulty breathing, pain or pressure in the chest, confusion, drowsiness, or weakness, they should seek follow-up care.

6.0 Management of Severe COVID-19

6.1 Oxygen Therapy and Monitoring

- ✓ **Give supplemental oxygen therapy immediately to patients with COVID-19 who have severe acute respiratory infection and respiratory distress, hypoxaemia or shock, and target saturations of 90-96% SpO₂ during resuscitation.**
- **Adults** with a worsening clinical presentation (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive airway management and oxygen therapy. Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO₂ ≥ 94% during resuscitation; or use face mask with reservoir bag (at 10-15 L/min) if the patient is in critical condition. Once the patient is stable, the target is > 90% SpO₂ in non-pregnant adults and ≥ 92–95% in pregnant patients (16,25).
- **Children** with a worsening clinical presentation (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive airway management and oxygen therapy during resuscitation to target SpO₂ ≥ 94%; otherwise, the target SpO₂ is ≥ 90% (25). The use of a nasal cannula is preferred in young children, as it may be better tolerated.
- All areas where patients with severe acute respiratory infection are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, face mask and mask with reservoir bag).

✔ **Closely monitor patients with COVID-19 for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis and respond immediately with supportive care interventions.**

- Patients hospitalized with COVID-19 require regular monitoring of vital signs and, where possible, use of early warning scores (e.g. NEWS2) that facilitate early recognition and escalation of a deteriorating patient (26). Deterioration in adults is often sudden and may occur in the second week of illness.
- In pregnant women sepsis is harder to assess. Use of a modified sepsis score, such as the modified early assessment warning system ([MEOWS](#)) is recommended (71).
- In adults, a complete blood count with differential, electrolytes, creatinine, liver enzymes, liver function tests and lactate should be done, as well as other clinically indicated blood tests, and an ECG should be performed at admission and as clinically indicated, to monitor for complications such as acute liver injury, acute kidney injury, acute cardiac injury or shock. Paediatric patients should have testing done as indicated by clinical judgement. Consider developing electronic order sets or pre-printed orders.
- Application of timely, effective and safe supportive therapies is the cornerstone of therapy for patients who develop severe manifestations of COVID-19.
- After resuscitation and stabilization of a pregnant patient, fetal well-being should be monitored.

✔ **Understand the patient's co-morbid conditions to tailor the management of critical illness.**

- Determine which chronic therapies should be continued and which should be stopped temporarily. Monitor for drug interactions.
- Metered dose inhalers with a spacer are preferred to nebulizers to reduce the potential to generate respiratory aerosols.

✔ **Use conservative fluid management in patients with severe acute respiratory infection when there is no evidence of shock.**

- Patients with severe acute respiratory disease should be treated cautiously with intravenous fluids, because aggressive fluid resuscitation may worsen oxygenation, especially in settings where there is limited availability of mechanical ventilation (27). This applies to the care of both children and adults.

6.2 Treatment of Co-infections

✔ **Give empiric antimicrobials to treat all likely pathogens causing severe acute respiratory infection and sepsis as soon as possible, within 1 hour of initial patient assessment for patients with sepsis.**

- Although the patient may be suspected to have COVID-19, administer appropriate empiric antimicrobials within **1 hour** of identification of sepsis (5). Empiric antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia or sepsis), local epidemiology and susceptibility data. The Infectious Disease Society of America and the American Thoracic Society have published treatment guidelines for community-acquired pneumonia that can be found at: https://www.idsociety.org/practice-guideline/practice-guidelines/#/name_na_str/ASC/0/+/. For paediatric cases guidance information can be found on the Canadian Paediatric Society website <https://www.cps.ca/en/documents>.
- When there is ongoing local circulation of influenza, empiric therapy with a neuraminidase inhibitor should be considered for the treatment of influenza viruses in patients with or at risk for severe disease (5).

✔ **De-escalate empiric therapy on the basis of microbiology results and clinical judgment.**

7.0 Management of Critical COVID-19

7.1 Acute Respiratory Distress Syndrome (ARDS)

✔ **Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy and prepare to provide advanced oxygen/ventilatory support.**

- Patients may continue to have increased work of breathing or hypoxemia even when oxygen is delivered via a face mask with reservoir bag (flow rates of 10–15 L/min, which is typically the minimum flow required to maintain bag inflation; FiO₂ 0.60–0.95). Hypoxemic respiratory failure in ARDS commonly results from intrapulmonary ventilation-perfusion mismatch or shunt and usually requires mechanical ventilation (5).

✔ **Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions.**

- Patients with ARDS, especially young children or those who are obese or pregnant, may desaturate quickly during intubation. Pre-oxygenate with 100% FiO₂ for 5 minutes, via a face mask with reservoir bag, bag-valve mask. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation, avoiding manual ventilation as a means to avoid aerosol generation, where possible and safe for patient care (28-30).

Recommendations for mechanically ventilated adult and paediatric patients with ARDS (5,31)

✔ **Implement mechanical ventilation using lower tidal volumes (4–8 mL/kg predicted body weight [PBW]) and lower inspiratory pressures (plateau pressure < 30 cmH₂O).**

- **Adults** – This is a strong recommendation from a clinical guideline for patients with ARDS (5), and is suggested for patients with sepsis-induced respiratory failure who do not meet ARDS criteria (5). The initial tidal volume is 6 mL/kg PBW; tidal volume up to 8 mL/kg PBW is allowed if undesirable side-effects occur (e.g. dyssynchrony, pH < 7.15). Permissive hypercapnia is permitted. Ventilator protocols are available (32). The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.
- **Children** - A lower level of plateau pressure (< 28 cmH₂O) is targeted, and a lower pH target is permitted (7.15–7.30). Tidal volumes should be adapted to disease severity: 3–6 mL/kg PBW in the case of poor respiratory system compliance, and 5–8 mL/kg PBW with better preserved compliance (31). Slightly higher Plateau pressures (30-32 cm H₂O) can be tolerated in case of poor chest wall compliance.

✔ **In adult patients with severe ARDS, prone ventilation for 12- 16 hours per day is recommended.**

- Application of prone ventilation is strongly recommended for adult patients, and may be considered for paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely (33,34). Protocols (including videos) are available at: <https://www.nejm.org/doi/full/10.1056/NEJMoa1214103>.
- Pregnant women should not be placed in a prone position but in the supine position with a wedge placed under the right hip to decrease aortocaval obstruction, or placed in lateral decubitus position.

✔ **Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.**

- This is a strong guideline recommendation for both adults and children (5); the main effect is to shorten the duration of ventilation. See reference (35) for a sample protocol.

! **In patients with moderate or severe ARDS, higher PEEP instead of lower PEEP is suggested.**

- PEEP titration requires consideration of benefits (reducing atelectrauma and improving alveolar recruitment) vs risks (end-inspiratory overdistension leading to lung injury and higher pulmonary vascular resistance). Tables are available to guide PEEP titration based on the FiO_2 required to maintain SpO_2 (32). Although high driving pressure (plateau pressure minus PEEP) may more accurately predict increased mortality in ARDS compared with high tidal volume or plateau pressure (36), data from RCTs of ventilation strategies that target driving pressure are not currently available.
- Recruitment manoeuvres (RMs) can be delivered as episodic periods of high continuous positive airway pressure (CPAP) (30–40 cmH_2O), progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs risks are similar. PEEP and RMs were both conditionally recommended in a clinical practice guideline. For PEEP, the guideline considered an individual patient data meta-analysis (37) of three RCTs. However, a subsequent RCT of high PEEP and prolonged high-pressure RMs showed harm, suggesting that the protocol in this RCT should be avoided (38). Monitoring of patients to identify those who respond to the initial application of higher PEEP or a different RM protocol, and stopping these interventions in non-responders are suggested (39).

! In patients with moderate-severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$), neuromuscular blockade by continuous infusion should not be routinely used.

- While one trial found that this strategy improved survival in adult patients with severe ARDS ($\text{PaO}_2/\text{FiO}_2 < 150$) without causing significant weakness (40), a results of a recent larger trial found that use of neuromuscular blockage with high PEEP strategy was not associated with a survival benefit when compared with a light sedation strategy without neuromuscular blockade (41). Continuous neuromuscular blockade may still be considered in patients, both adults and children, with ARDS in certain situations, such as ventilator dyssynchrony despite sedation, such that tidal volume limitation cannot be reliably achieved; refractory hypoxemia; or hypercapnia.

✗ Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis.

✓ Use in-line catheters for airway suctioning and clamp the endotracheal tube when disconnection is required (e.g., transfer to a transport ventilator).

Recommendations for adult and paediatric patients with ARDS who are treated with non-invasive or high flow oxygen systems

! High-flow nasal oxygen (HFNO) and non-invasive ventilation (NIV) should be considered. Patients treated with either HFNO or NIV should be closely monitored for clinical deterioration.

Remarks

- Adult HFNO systems can deliver 60 L/min of gas flow and FiO_2 up to 1.0. Paediatric circuits generally only handle up to 25 L/min, and many children will require an adult circuit to deliver adequate flow.
- Compared with standard oxygen therapy, HFNO reduces the need for intubation (42). Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary edema), hemodynamic instability, multiorgan failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia (42-44). Patients receiving HFNO should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Evidence-based guidelines on the treatment of

patients with COVID-19 with HFNO do not exist, and reports on HFNO in other coronavirus-infected patients are limited (44).

- NIV guidelines make no recommendation for use in hypoxemic respiratory failure (apart from cardiogenic pulmonary edema and post-operative respiratory failure) or pandemic viral illness (5). Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate in patients with other viral infections such as MERS who receive NIV (45).
- Patients receiving a trial of NIV should be in a monitored setting and cared for by experienced personnel capable of endotracheal intubation in case the patient acutely deteriorates or does not improve after a short trial (about 1 hour). Patients with haemodynamic instability, multiorgan failure, or abnormal mental status should likely not receive NIV in place of other options such as invasive ventilation.
- In situations where mechanical ventilation may not be available, bubble nasal CPAP may be used for newborns and children with severe hypoxemia (46).

Recommendations for adult and paediatric patients with ARDS in whom a lung protective ventilation strategy fails

! In settings with access to expertise in extracorporeal membrane oxygenation (ECMO), consider referral of patients who have refractory hypoxemia despite lung protective ventilation.

- An RCT of ECMO for adult patients with ARDS was stopped early and found no statistically significant difference in the primary outcome of 60-day mortality between ECMO and standard medical management (including prone positioning and neuromuscular blockade) (47). However, ECMO was associated with a reduced risk of the composite outcome of mortality and crossover to ECMO (47), and a post hoc Bayesian analysis of this RCT showed that ECMO is very likely to reduce mortality across a range of prior assumptions (48). In patients with MERS, ECMO vs conventional treatment was associated with reduced mortality in a cohort study (49). ECMO should ideally be offered in expert centres with a sufficient case volume to maintain expertise and that can apply the IPC measures required for adult and paediatric COVID-19 patients (50,51).

7.2 Septic Shock

✓ Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) \geq 60 mmHg AND lactate is \geq 2 mmol/L, in absence of hypovolemia.

✓ Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] < 5th centile or 2 SD below normal for age) or two or more of the following: altered mental state; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or feeble pulses; tachypnea; mottled or cool skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.

- In the absence of a lactate measurement, use blood pressure (i.e. MAP) and clinical signs of perfusion to define shock.
- Standard care includes early recognition and the following treatments within 1 hour of recognition: antimicrobial therapy and initiation of fluid bolus and vasopressors for hypotension (5). The use of central venous and arterial catheters should be based on resource availability and individual patient needs. Detailed guidelines are available for the management of septic shock in adults (5) and children (6,16). Alternate fluid regimens are suggested when caring for adults and children in resource-limited settings (56,57).

Recommendations for resuscitation strategies for adult and paediatric patients with septic shock.

✔ In resuscitation for septic shock in *adults*, give 250-500 mL crystalloid fluid as a rapid bolus in the first 15-30 minutes and reassess for signs of fluid overload after each bolus.

✔ In resuscitation for septic shock in *children*, give 10-20 mL/kg crystalloid fluid as a rapid bolus in the first 30-60 minutes and reassess for signs of fluid overload after each bolus.

! Fluid resuscitation may lead to volume overload, including respiratory failure, particularly with ARDS. If there is no response to fluid loading or signs of volume overload appear (e.g. jugular venous distension, crackles on lung auscultation, pulmonary edema on imaging, or hepatomegaly in children), then reduce or discontinue fluid administration. This step is particularly important in patients with hypoxemic respiratory failure.

- Crystalloids include normal saline and Ringer’s lactate.
- Determine need for additional fluid boluses (250–500 mL in adults or 10–20 mL/kg in children) based on clinical response and improvement of perfusion targets. Perfusion targets include MAP (> 65 mmHg or age-appropriate targets in children), urine output (> 0.5 mL/kg/hr in adults, 1 mL/kg/hr in children), and improvement of skin mottling and extremity perfusion, capillary refill, heart rate, level of consciousness, and lactate.
- Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience (5). These indices include passive leg raises, fluid challenges with serial stroke volume measurements, or variations in systolic pressure, pulse pressure, inferior vena cava size, or stroke volume in response to changes in intrathoracic pressure during mechanical ventilation.
- In pregnant women, compression of the inferior vena cava can cause a decrease in venous return and cardiac preload and may result in hypotension. For this reason, pregnant women should be cared for with a wedge under their right hip and may need to be placed in a lateral decubitus position to off-load the inferior vena cava (58).
- Clinical trials conducted in resource limited studies comparing aggressive versus conservative fluid regimens suggest higher mortality in patients treated with aggressive fluid regimes for other severe infections (56,57).

✘ **Do not use hypotonic crystalloids, starches or gelatins for resuscitation.**

- Starches are associated with an increased risk of death and acute kidney injury compared with crystalloids. The effects of gelatins are less clear, but they are more expensive than crystalloids (5,59). Hypotonic (vs isotonic) solutions are less effective at increasing intravascular volume. *Surviving Sepsis* also suggests albumin for resuscitation when patients require substantial amounts of crystalloids, but this conditional recommendation is based on low-quality evidence (5).

✔ **In adults, administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is MAP ≥ 60 mmHg in adults and improvement of markers of perfusion.**

✔ **In children administer vasopressors if:**

- there are signs of shock such as altered mental state; tachycardia or bradycardia (HR < 90 bpm or > 160 bpm in infants and HR < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 seconds) or feeble pulses; tachypnea; mottled cool skin or petechial or purpuric rash; increased lactate; persisting oliguria after 2 boluses; or

- age-appropriate blood pressure targets are not achieved; or
- signs of fluid overload are apparent (6).

! If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and monitor closely for signs of extravasation and local tissue necrosis. If extravasation occurs, stop the infusion. Vasopressors can also be administered through intraosseous needles.

! If signs of poor perfusion and cardiac dysfunction persist despite achieving the MAP target with fluids and vasopressors, consider an inotrope such as dobutamine.

- Vasopressors (i.e. norepinephrine, epinephrine, vasopressin, and dopamine) are most safely given through a central venous catheter at a strictly controlled rate, but it is also possible to administer them safely via peripheral vein (60) and intraosseous needle. Monitor blood pressure frequently and titrate the vasopressor to the minimum dose necessary to maintain perfusion and prevent side effects.
- Norepinephrine is considered first-line in adult patients; epinephrine or vasopressin can be added to achieve the MAP target. Because of the risk of tachyarrhythmia, reserve dopamine for selected patients with low risk of tachyarrhythmia or those with bradycardia.
- In children, epinephrine is considered first-line treatment, while norepinephrine can be added if shock persists despite optimal dose of epinephrine.
- No RCTs have compared dobutamine with placebo for clinical outcomes
- See [Section 9.0](#) for remarks on corticosteroids and sepsis.

7.3 Prevention of Complications

Implement the interventions shown in Table 2 below to prevent complications associated with critical illness. These interventions are based on *Surviving Sepsis* (5) and other guidelines (52-55) and are considered to be feasible and based on high quality evidence.

TABLE 2 – PREVENTION OF COMPLICATIONS IN CRITICALLY ILL PATIENTS

Anticipated outcome	Interventions
Reduce days of invasive mechanical ventilation	<ul style="list-style-type: none"> • Use weaning protocols that include daily assessment for readiness to breathe spontaneously. • Minimize continuous or intermittent sedation, targeting specific titration endpoints (sedation score targeted light sedation unless contraindicated) or with daily interruption of continuous sedative infusions.
Reduce incidence of ventilator-associated pneumonia	<ul style="list-style-type: none"> • Oral intubation is preferable to nasal intubation in adolescents and adults. • Keep patient in semi-recumbent position (head of bed elevation at 30–45°) • Use a closed suctioning system; periodically drain and discard condensate in tubing. • Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged, but not routinely. • Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days.
Reduce incidence of venous thromboembolism	<ul style="list-style-type: none"> • Use pharmacological prophylaxis (low molecular-weight heparin [preferred] or heparin subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices),

Anticipated outcome	Interventions
Reduce incidence of catheter-related bloodstream infection	<ul style="list-style-type: none"> Use a checklist with completion verified by a real-time observer as a reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed.
Reduce incidence of pressure ulcers	<ul style="list-style-type: none"> Turn patient every 2 hours, unless contraindicated by patient condition or use of prone positioning.
Reduce incidence of stress ulcers and gastrointestinal bleeding	<ul style="list-style-type: none"> Give early enteral nutrition (within 24–48 hours of admission). Consider administering histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for gastrointestinal bleeding include mechanical ventilation for ≥ 48 hours, coagulopathy, renal replacement therapy, liver disease, multiple comorbidities, and higher organ failure score.
Reduce incidence of ICU-related weakness	<ul style="list-style-type: none"> Actively mobilize the patient early in the course of illness when safe to do so.

8.0 Special Considerations

8.1 Caring for Pregnant Women with COVID-19

To date, there are limited data on clinical presentation and perinatal outcomes after COVID-19 during pregnancy or the post-partum period. There is no evidence that pregnant women present with different signs or symptoms or are at higher risk of severe illness.

✔ **Pregnant and recently pregnant women with suspected or confirmed COVID-19 should be treated with the supportive and management therapies previously described for other adults, taking into account the immunologic and physiologic adaptations occurring during and after pregnancy.**

Evidence of increased severe maternal or neonatal outcomes is uncertain, and limited to infection in the third trimester, with some cases of premature rupture of membranes, fetal distress and preterm birth reported. There was one case of stillbirth and one case of neonatal death in 38 cases from China. (68,69).

✔ **Pregnant women with a suspected, probable or confirmed COVID-19 infection, including women who may need to spend time in isolation, should have access to woman-centred, respectful skilled care, including obstetric, foetal medicine and neonatal care, as well as mental health and psychosocial support, with readiness to care for maternal and neonatal complications.**

- Prevention of complications as described earlier, also apply to pregnant and recently pregnant women including those with miscarriage, late pregnancy fetal loss and postpartum/post-abortion women.
- The mode of delivery should be individualized based on obstetric indications.
- Multidisciplinary consultations from obstetric, perinatal, neonatal, infectious disease and intensive care specialists should be provided as required.

✔ **All recently pregnant women with COVID-19 infection or who have recovered from COVID-19 should be provided with counselling on safe infant feeding and appropriate infection prevention measures to prevent COVID-19 transmission.**

- ✓ **At this point, there is no evidence that pregnant women present with increased risk of severe illness. Pregnant and recently pregnant women who have recovered from COVID-19 should be encouraged to attend routine antenatal, postpartum or other obstetrical care as appropriate. Enhanced fetal surveillance is recommended for women with COVID-19 illness.** The SOGC has published several resources to assist obstetricians in Canada in dealing with COVID-19, which can be found on their website at <https://sogc.org/>.

8.2 Caring for Infants and Mothers with COVID-19 – IPC and Breastfeeding

Relatively few cases have been reported of infants confirmed with COVID-19 infection. At this time there is no clear evidence that vertical transmission may occur. Breast milk samples from the mothers after the first lactation were also all negative for the COVID-19 virus (68,69).

- ✓ **Infants born to mothers with suspected, probable, or confirmed COVID-19 should be fed according to standard infant feeding guidelines while providing necessary infection prevention precautions.**
- ✓ **Symptomatic mothers who are breastfeeding should practice respiratory hygiene, including during feeding (for example, use of a mask when near a child if the mother has respiratory symptoms), perform hand hygiene before and after contact with the child, and routinely clean and disinfect surfaces with which the symptomatic mother has been in contact.**
- ✓ **In situations when severe illness in a mother due to COVID-19 or other complications prevents her from caring for her infant or prevents her from continuing direct breastfeeding, mothers should be encouraged and supported to express milk, and safely provide breast milk to the infant, while applying appropriate IPC measures.**
- ✓ **Mothers and infants should be allowed to remain together and to practice rooming-in if desired, especially during establishment of breastfeeding, whether they or their infants have suspected, probable or confirmed COVID-19.**
- ✓ **Parents and caregivers who may need to be separated from their children, and children who may need to be separated from their primary caregivers, should have access to appropriately trained health or non-health workers for mental health and psychosocial support.**

8.3 Caring for Older Persons with COVID-19

Older age and comorbid conditions such as diabetes and cardiovascular disease have been reported as risk factors for death in persons with COVID-19 (4). Older persons are at highest risk for severe disease and fatality and are one of the most vulnerable populations.

- ✓ **For older persons with probable or suspected COVID-19, in addition to a conventional history the assessment should include an understanding of the person's life, values, priorities and preferences for health management.**
- ✓ **Ensure multidisciplinary collaboration (physicians, nurses, pharmacists and other health professionals) in the decision-making process to address multimorbidity and functional decline.**
- ✓ **Early detection of inappropriate medication prescriptions is recommended to prevent adverse drug events and drug interactions in those being treated for COVID-19.** Older patients are at greater risk of polypharmacy which increases the risk of negative health consequences.

- ✔ **Involve caregivers and family members in decision-making and goal setting throughout the management of older COVID-19 patients.**
- ✔ **Symptom -based and palliative care should be made available as appropriate.**

8.4 Managing Patients with COVID-19 in Remote and Isolated Communities

While primary health care services are available in most remote and isolated communities, they have limited capacity to provide acute care and may lack appropriate medical equipment, supplies and services (e.g., ventilators, access to specialists) to treat patients with severe illness. In many remote and isolated communities, a nurse-led health care team can provide emergency resuscitation and stabilization, emergency ambulatory care and out-patient non-urgent services. Access to physician services is available remotely via telehealth or teleconference, but much variation exists from community to community regarding the availability and frequency of physicians. Severely ill patients requiring complex emergency medical care are evacuated to a secondary or tertiary hospital or facility.

Treatment considerations for these remote and isolated settings include the following measures:

- Primary care providers or nursing stations, where available, should plan to provide triage and assessment, primary care treatment and monitoring.
- Mild disease, including uncomplicated pneumonia, should be managed within the community, with appropriate precautions in place.
- Alternate arrangements for self-isolation may be needed for persons in crowded living arrangements.
- Fluid management should be conservative when there is no evidence of shock, because aggressive fluid management may worsen oxygenation in settings without access to mechanical ventilation.
- Mild cases may progress to lower respiratory tract disease. Possible risk factors for progression to severe illness include older age and underlying chronic medical conditions such as lung disease, cancer, heart failure, cerebrovascular disease, renal disease, liver disease, diabetes, immunocompromising conditions, and pregnancy (3,70).
- Patients should be carefully monitored for signs of impending deterioration so that transfer can be arranged before intubation is required.
- Anticipate delays to access hospital care (awaiting air-ambulance, weather issues). Therefore, a low threshold should be considered for medevac options, particularly for the elderly, persons with underlying medical conditions or persons with evidence of pneumonia.

9.0 Specific and Adjunctive COVID-19 Treatments and Clinical Research

There is no current evidence to recommend any specific anti-COVID-19 treatment for patients with confirmed COVID-19. There are many ongoing clinical trials testing various potential medical counter measures. Until specific therapies become available, any medication should be given as part of a randomized controlled trial.

- ✔ **Collect standardized clinical data on all hospitalized patients to improve our understanding of the natural history of disease.**
- ✔ **Use of investigational anti-COVID-19 therapeutics should be done under ethically approved, randomized, controlled trials.**
- ✘ **Do not routinely give systemic corticosteroids for treatment of viral pneumonia outside of clinical trials.**

- A systematic review of observational studies of corticosteroids administered to patients with SARS reported no survival benefit and possible harms (avascular necrosis, psychosis, diabetes, and delayed viral clearance) (62). A systematic review of observational studies in influenza found a higher risk of mortality and secondary infections with corticosteroids; the evidence was judged as very low to low quality due to confounding by indication (63). A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality (64). Finally, a recent study of patients receiving corticosteroids for MERS used a similar statistical approach and found no effect of corticosteroids on mortality but delayed LRT clearance of MERS-CoV (65). Given the lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. Other reasons may include exacerbation of asthma or COPD, septic shock, and risk and benefit analysis needs to be conducted for individual patients.
- A recent guideline that incorporates the findings of two recent large RCTs makes a weak recommendation for corticosteroids for all patients with sepsis (including septic shock) (66). *Surviving Sepsis* guidelines, written before these RCTs were reported, recommend corticosteroids only for patients in whom adequate fluids and vasopressor therapy do not restore hemodynamic stability (5).
- Clinicians considering corticosteroids for a patient with COVID-19 and sepsis must balance the potential small reduction in mortality with the potential downside of prolonged shedding of coronavirus in the respiratory tract, as has been observed in patients with MERS (65). If corticosteroids are prescribed, monitor and treat hyperglycemia, hypernatremia and hypokalemia. Monitor for recurrence of inflammation and signs of adrenal insufficiency after stopping corticosteroids, which may have to be tapered.
- **Pregnant women** – The Society of Obstetricians and Gynaecologists of Canada (SOGC) recommends antenatal corticosteroid therapy for fetal lung maturation in women who are between 24+0 and 34+6 weeks of gestation if delivery is anticipated in the next 7 days. The recommended dosage of steroid is low and is unlikely to impact management of maternal disease but is of significant benefit to the fetus/infant. The SOGC clinical practice guideline can be found on their website at: <https://www.sogc.org/en/content/guidelines-jogc/guidelines-and-jogc.aspx?hkey=aa09f753-7812-462a-9d80-3e6b609f6ec6>. In cases where the woman presents with mild COVID-19 infection, the clinical benefits of antenatal corticosteroid will outweigh the risks of potential harm to the mother. In the situation of severe maternal disease, the balance of benefits and harms for the woman and the preterm newborn should be discussed with the woman to ensure an informed decision.
- WHO has prioritized the evaluation of corticosteroids in clinical trials to assess safety and efficacy in COVID-19 treatment (Link: <https://www.who.int/blueprint/priority-diseases/key-action/novel-coronavirus/en/>).

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