



Health & Family Welfare Department, Government of Tamil Nadu

TNSOP - 6
GUIDELINES FOR CLINICAL MANAGEMENT OF COVID-19

CLINICAL SYNDROMES ASSOCIATED WITH COVID - 19 INFECTION

Uncomplicated cases:

Patients with uncomplicated upper respiratory tract viral infection, may have non-specific symptoms such as fever, cough, sore throat, nasal congestion, malaise, headache. The elderly and immunosuppressed may present with atypical symptoms. These patients do not have any signs of dehydration, sepsis or shortness of breath.

SARI (Severe Acute Respiratory Illness):

An ARI with history of fever or measured temperature $\geq 38^{\circ}\text{C}$ and cough; onset within the last ~10 days; and requiring hospitalization.

Surveillance case definitions for SARI:

1. SARI in a person, with history of fever and cough requiring admission to hospital, with no other etiology that fully explains the clinical presentation (clinicians should also be alert to the possibility of atypical presentations in patients who are immune-compromised);

AND any of the following:

- a) A history of international travel in 14 days prior to symptom onset; or
 - b) The disease occurs in a health care worker who has been working in an environment where patients with severe acute respiratory infections are being cared for, without regard to place of residence or history of travel; or
 - c) The person develops an unusual or unexpected clinical course, especially sudden deterioration despite appropriate treatment, without regard to place of residence or history of travel, even if another etiology has been identified that fully explains the clinical presentation
2. A person with acute respiratory illness of any degree of severity who, within 14 days before onset of illness, had any of the following exposures:
 - a) close physical contact² with a confirmed case of COVID - 19 infection, while that patient was symptomatic; or
 - b) a healthcare facility in a country where hospital-associated COVID - 19 infections have been reported;

Mild pneumonia:

Patient with pneumonia and no signs of severe pneumonia. Child with non-severe pneumonia has cough or difficulty in breathing/ fast breathing: (fast breathing - in breaths/min): <2 months, ≥ 60 ; 2 –11 months, ≥ 50 ; 1 –5 years, ≥ 40 and no signs of severe pneumonia.

Severe pneumonia:

Adolescent or adult: fever or suspected respiratory infection, plus one of the following;

- respiratory rate >30 breaths/min,
- severe respiratory distress,
- SpO₂ $<90\%$ on room air

Child with cough or difficulty in breathing, plus at least one of the following:

- central cyanosis or SpO₂ <90%;
- severe respiratory distress (e.g. grunting, chest in-drawing);
- signs of pneumonia with any of the following danger signs:
 - inability to breastfeed or drink,
 - lethargy or unconsciousness, or convulsions.
- Other signs of pneumonia may be present:
 - chest indrawing,
 - fast breathing (in breaths/min): <2 months ≥60; 2 –11 months ≥50; 1–5 years ≥40.

The diagnosis is clinical; chest imaging can exclude complications.

Acute Respiratory Distress Syndrome:

Onset: new or worsening respiratory symptoms within one week of known clinical insult.

Chest imaging (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by effusions, lobar or lung collapse, or nodules.

Origin of oedema: respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of oedema if no risk factor present.

Sepsis:

Adults: life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection, with organ dysfunction. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, 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~~ SIRS criteria, of which one must be abnormal temperature or white blood cell count

Septic shock:

Adults: persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level < 2 mmol/L

Children: any hypotension (SBP < 5 th centile or > 2 SD below normal for age) or 2-3 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 warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia

EARLY SUPPORTIVE THERAPY AND MANAGEMENT

- a) Give supplemental oxygen therapy immediately to patients with SARI and respiratory distress, hypoxaemia, or shock: Initiate oxygen therapy at 5 L/min and titrate flow rates to reach target SpO₂ $\geq 90\%$ in non -pregnant adults and SpO₂ $\geq 92 - 95\%$ in pregnant patients.
- b) Children with emergency signs (obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma or convulsions) should receive oxygen therapy during resuscitation to target SpO₂ $\geq 94\%$; otherwise, the target SpO₂ is $\geq 90\%$.
- c) All areas where patients with SARI are cared for should be equipped with pulse oximeters, functioning oxygen systems and disposable, single-use, oxygen-delivering interfaces (nasal cannula, simple face mask, and mask with reservoir bag). Use contact precautions when handling contaminated oxygen interfaces of patients with COVID – 19.
- d) Use conservative fluid management in patients with SARI when there is no evidence of shock: Patients with SARI 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.

- e) Give empiric antimicrobials to treat all likely pathogens causing SARI. Give antimicrobials within one hour of initial patient assessment for patients with sepsis: Although the patient may be suspected to have COVID - 19, Administer appropriate empiric antimicrobials within ONE hour of identification of sepsis. Empirical antibiotic treatment should be based on the clinical diagnosis (community-acquired pneumonia, health care-associated pneumonia [if infection was acquired in healthcare setting], or sepsis), local epidemiology and susceptibility data, and treatment guidelines. Empirical therapy includes a neuraminidase inhibitor for treatment of influenza when there is local circulation or other risk factors, including travel history or exposure to animal influenza viruses. Empirical therapy should be de-escalated on the basis of microbiology results and clinical judgment
- f) Do not routinely give systemic corticosteroids for treatment of viral pneumonia or ARDS outside of clinical trials unless they are indicated for another reason: 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). 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. A subsequent study that addressed this limitation by adjusting for time-varying confounders found no effect on mortality. 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 lower respiratory tract (LRT) clearance of MERS-CoV. Given lack of effectiveness and possible harm, routine corticosteroids should be avoided unless they are indicated for another reason. See section F for the use of corticosteroids in sepsis.
- g) Closely monitor patients with SARI for signs of clinical deterioration, such as rapidly progressive respiratory failure and sepsis, and apply supportive care interventions immediately: Application of timely, effective, and safe supportive therapies is the cornerstone of therapy for patients that develop severe manifestations of COVID – 19.

- h) Understand the patient's co-morbid condition(s) to tailor the management of critical illness and appreciate the prognosis: During intensive care management of SARI, determine which chronic therapies should be continued and which therapies should be stopped temporarily.
- i) Communicate early with patient and family: Communicate pro-actively with patients and families and provide support and prognostic information. Understand the patient's values and preferences regarding life-sustaining interventions.

MANAGEMENT OF HYPOXIC RESPIRATORY FAILURE AND ARDS

- a) Recognize severe hypoxemic respiratory failure when a patient with respiratory distress is failing standard oxygen therapy. 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.
- b) High – flow nasal catheter oxygenation or non – invasive mechanical ventilation: When respiratory distress and/or hypoxemia of the patient cannot be alleviated after receiving standard oxygen therapy, high – flow nasal cannula oxygen therapy or non – invasive ventilation can be considered. If conditions do not improve or even get worse within a short time (1 – 2 hours), tracheal intubation and invasive mechanical ventilation should be used in a timely manner. Compared to standard oxygen therapy, HFNO reduces the need for intubation. Patients with hypercapnia (exacerbation of obstructive lung disease, cardiogenic pulmonary oedema), hemodynamic instability, multi-organ 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 hypercapnia²⁵. 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 hr).

- c) NIV guidelines make no recommendation on use in hypoxemic respiratory failure (apart from cardiogenic pulmonary oedema and post-operative respiratory failure) or pandemic viral illness (referring to studies of SARS and pandemic influenza). Risks include delayed intubation, large tidal volumes, and injurious transpulmonary pressures. Limited data suggest a high failure rate when MERS patients received NIV. 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 hr). Patients with hemodynamic instability, multiorgan failure, or abnormal mental status should not receive NIV.
- d) Recent publications suggest that newer HFNO and NIV systems with good interface fitting do not create widespread dispersion of exhaled air and therefore should be associated with low risk of airborne transmission.
- e) 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 de-saturate quickly during intubation. Pre-oxygenate with 100% FiO₂ for 5 minutes, via a face mask with reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation.
- f) Implement mechanical ventilation using lower tidal volumes (4–8 ml/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure <30 cmH₂O). This is a strong recommendation from a clinical guideline for patients with ARDS, and is suggested for patients with sepsis-induced respiratory failure. 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). Hypercapnia is permitted if meeting the pH goal of 7.30- 7.45. Ventilator protocols are available. The use of deep sedation may be required to control respiratory drive and achieve tidal volume targets.
- g) In patients with severe ARDS, prone ventilation for >12 hours per day is recommended. Application of prone ventilation is strongly recommended for adult

and paediatric patients with severe ARDS but requires sufficient human resources and expertise to be performed safely.

- h) Use a conservative fluid management strategy for ARDS patients without tissue hypoperfusion.
- i) 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 FiO₂ required to maintain SpO₂. A related intervention of recruitment manoeuvres (RMs) is delivered as episodic periods of high continuous positive airway pressure [30–40 cm H₂O], progressive incremental increases in PEEP with constant driving pressure, or high driving pressure; considerations of benefits vs. risks are similar. Higher PEEP and RMs were both conditionally recommended in a clinical practice guideline. In patients with moderate-severe ARDS (PaO₂/FiO₂ <150), neuromuscular blockade by continuous infusion should not be routinely used.
- j) In settings with access to expertise in extracorporeal life support (ECLS), consider referral of patients with refractory hypoxemia despite lung protective ventilation. ECLS should only be offered in expert centres with a sufficient case volume to maintain expertise and that can apply the IPC measures required for COVID – 19 patients
- k) Avoid disconnecting the patient from the ventilator, which results in loss of PEEP and atelectasis. Use in-line catheters for airway suctioning and clamp endotracheal tube when disconnection is required (for example, transfer to a transport ventilator)

Oxygenation (adults):

- Mild ARDS: 200 mmHg < PaO₂/FiO₂ ≤ 300 mmHg (with PEEP or CPAP ≥5 cm H₂O, or non-ventilated)

- Moderate ARDS: $100 \text{ mmHg} < \text{PaO}_2/\text{FiO}_2 \leq 200 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$, or non-ventilated)
- Severe ARDS: $\text{PaO}_2/\text{FiO}_2 \leq 100 \text{ mmHg}$ with $\text{PEEP} \geq 5 \text{ cm H}_2\text{O}$, or non-ventilated)
- When PaO_2 is not available, $\text{SpO}_2/\text{FiO}_2 \leq 315$ suggests ARDS (including in non-ventilated patients)

Oxygenation (children):

- Bilevel NIV or CPAP $\geq 5 \text{ cm H}_2\text{O}$ 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 $\text{OSI} \geq 12.3$

* note OI = Oxygenation Index and OSI = Oxygenation Index using SpO_2)

Management of septic shock

- Recognize septic shock in adults when infection is suspected or confirmed AND vasopressors are needed to maintain mean arterial pressure (MAP) $\geq 65 \text{ mmHg}$ AND
- lactate is $< 2 \text{ mmol/L}$, in absence of hypovolemia. Recognize septic shock in children with any hypotension (systolic blood pressure [SBP] $< 5^{\text{th}}$ centile or $> 2 \text{ SD}$ below normal for age) or 2-3 of the following: altered mental state; tachycardia or bradycardia (HR $< 90 \text{ bpm}$ or $> 160 \text{ bpm}$ in infants and HR $< 70 \text{ bpm}$ or $> 150 \text{ bpm}$ in children); prolonged capillary refill ($> 2 \text{ sec}$) or warm vasodilation with bounding pulses; tachypnea; mottled skin or petechial or purpuric rash; increased lactate; oliguria; hyperthermia or hypothermia.
- In the absence of a lactate measurement, use 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 fluid loading and vasopressors for hypotension. 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 and children.

- d) In resuscitation from septic shock in adults, give at least 30 ml/kg of isotonic crystalloid in adults in the first 3 hours. In resuscitation from septic shock in children in well-resourced settings, give 20 ml/kg as a rapid bolus and up to 40-60 ml/kg in the first 1 hr. Do not use hypotonic crystalloids, starches, or gelatins for resuscitation.
- e) Fluid resuscitation may lead to volume overload, including respiratory failure. If there is no response to fluid loading and signs of volume overload appear (for example, jugular venous distension, crackles on lung auscultation, pulmonary oedema on imaging, or hepatomegaly in children), then reduce or discontinue fluid administration. This step is particularly important where mechanical ventilation is not available. Alternate fluid regimens are suggested when caring for children in resource-limited settings.
- f) Crystalloids include normal saline and Ringer's lactate. Determine need for additional fluid boluses (250-1000 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, capillary refill, level of consciousness, and lactate. Consider dynamic indices of volume responsiveness to guide volume administration beyond initial resuscitation based on local resources and experience. 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.
- g) Administer vasopressors when shock persists during or after fluid resuscitation. The initial blood pressure target is $MAP \geq 65$ mmHg in adults and age-appropriate targets in children.
- h) If central venous catheters are not available, vasopressors can be given through a peripheral IV, but use a large vein and closely monitor for signs of extravasation and local tissue necrosis. If extravasation occurs, stop infusion. Vasopressors can also be administered through intraosseous needles.

- i) If signs of poor perfusion and cardiac dysfunction persist despite achieving MAP target with fluids and vasopressors, consider an inotrope such as dobutamine

OTHER THERAPEUTIC MEASURES

- a) For patients with progressive deterioration of oxygenation indicators, rapid worsening on imaging and excessive activation of the body’s inflammatory response, glucocorticoids can be used for a short period of time (3 to 5 days).
- b) It is recommended that dose should not exceed the equivalent of methylprednisolone 1 – 2mg/kg/day. Note that a larger dose of glucocorticoid will delay the removal of coronavirus due to immunosuppressive effects.
- c) For pregnant severe and critical cases, pregnancy should be preferably terminated. Consultations with obstetric, neonatal, and intensive care specialists (depending on the condition of the mother) are essential. Patients often suffer from anxiety and fear and they should be supported by psychological counselling.

PREVENTION OF COMPLICATION

Implement the following interventions to prevent complications associated with critical illness.

These interventions are based on Surviving Sepsis or other guidelines, and are generally limited to feasible recommendations based on high quality evidence.

Anticipated Outcome	Interventions
Reduce days of invasive mechanical ventilation	Use weaning protocols that include daily assessment for readiness to breathe spontaneously Minimize continuous or intermittent sedation, targeting specific titration endpoints (light sedation unless contraindicated) or with daily interruption of continuous sedative infusions

<p>Reduce incidence of ventilator associated pneumonia</p>	<p>Oral intubation is preferable to nasal intubation in adolescents and adults</p> <p>Keep patient in semi-recumbent position (head of bed elevation 30-45°)</p> <p>Use a closed suctioning system; periodically drain and discard condensate in tubing</p> <p>Use a new ventilator circuit for each patient; once patient is ventilated, change circuit if it is soiled or damaged but not routinely</p> <p>Change heat moisture exchanger when it malfunctions, when soiled, or every 5–7 days</p>
<p>Reduce incidence of venous thromboembolism</p>	<p>Use pharmacological prophylaxis (low molecular-weight heparin [preferred if available] or heparin 5000 units subcutaneously twice daily) in adolescents and adults without contraindications. For those with contraindications, use mechanical prophylaxis (intermittent pneumatic compression devices).</p>
<p>Reduce incidence of catheter related bloodstream infection</p>	<p>Use a checklist with completion verified by a real-time observer as reminder of each step needed for sterile insertion and as a daily reminder to remove catheter if no longer needed</p>
<p>Reduce incidence of pressure ulcers</p>	<p>Turn patient every two hours</p>
<p>Reduce incidence of stress ulcers and gastrointestinal bleeding</p>	<p>Give early enteral nutrition (within 24–48 hours of admission)</p> <p>Administer histamine-2 receptor blockers or proton-pump inhibitors in patients with risk factors for GI bleeding. Risk factors for gastrointestinal bleeding include mechanical ventilation ≥ 48 hours, coagulopathy, renal replacement therapy, liver</p>

	disease, multiple co-morbidities, and higher organ failure score
Reduce incidence of ICU-related weakness	Actively mobilize the patient early in the course of illness when safe to do so

SPECIFIC COVID-19 TREATMENTS AND CLINICAL RESEARCH

There is no current evidence from RCTs to recommend any specific treatment for suspected or confirmed patients with COVID - 19. No specific anti-virals are recommended for treatment of COVID – 19 due to lack of adequate evidence from literature

. The use of Lopinavir/ Ritonavir in PEP regimens for HIV (4 weeks) is also associated with significant adverse events which many a times leads to discontinuation of therapy. In light of the above, Lopinavir/ Ritonavir should **ONLY** be used with proper informed expressed consent on a case to case basis for severe cases, within the under-mentioned framework along with supportive treatment as per need.

a) Administration of Lopinavir/ Ritonavir

Administration of Lopinavir/ Ritonavir to be considered in Lab confirmed cases of COVID – 19 when the following criteria are met:

Symptomatic patients with any of the following:

- i. hypoxia,
- ii. hypotension,
- iii. new onset organ dysfunction (one or more)
 - Increase in creatinine by 50% from baseline, GFR reduction by >25% from baseline or urine output of <0.5 ml/kg for 6 hours.
 - Reduction of GCS by 2 or more
 - Any other organ dysfunction

iv. High Risk Groups:

- Age > 60 yrs
- Diabetes Mellitus, Renal Failure, Chronic Lung disease
- Immuno – compromised persons

Dosage:

- i. Lopinavir/ Ritonavir (200 mg/ 50 mg) – 2 tablets twice daily
- ii. For patients unable to take medications by mouth: Lopinavir 400mg/ Ritonavir 100 mg – 5ml suspension twice daily

Duration: 14 days or for 7 days after becoming asymptomatic.

b) Support to Treating Physicians

For any queries, contact RGGGH in contact number – 044 25305715/
8939797696.

Discharge policy:

Discharge after chest radiograph has cleared and two specimens for COVID-19 turn negative 24 hours apart and clinically stable.