Bangladesh Society of Medicine

Clinical Guidelines for the Management of Moderate to Severe COVID-19 Disease – Bangladesh Model

Joint Collaboration of Australian and Bangladeshi COVID-19 Frontline Physicians

Version 2

22nd June ,2020

Dedicated to the Memory of Late Dr Moyeen Uddin – The 1st COVID-19 Martyr Physician of Bangladesh
A great clinician and benevolent human being

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Society of Medicine

We are for comprehensive patient care and education

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Disclaimer

The COVID-19 Management Guidelines-Bangladesh Model has been developed to assist clinicians (Internal Medicine, Pulmonologist and Critical Care Medicine) to prepare and plan clinical care services in the event of a pandemic, to provide a safe working environment for staff and patients and to give guidance on the identification and treatment of patients with COVID-19 infection. The recommendations have been put together by a team of specialists- Respiratory, Internal medicine, Infectious disease, Immunology and Intensive Care doctors from Australia and Bangladesh who are directly involved in COVID-19 management. The authors have made considerable effort to ensure the information contained within the recommendations is correct at the time of publication. Information provided has been sourced from the best available evidence and expert opinions. This recommendation entails changes from international recommendations due to extremely limited resources in Bangladesh. Further iterations of these guidelines will be published as new information comes to hand. The Society accepts no responsibility for any inaccuracies, information perceived as misleading, or the success or failure of any of the recommendations detailed in the document. The information in this document cannot replace professional advice.

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Stages of COVID-19 illness

- **Asymptomatic:** Individuals who test positive for SARS-CoV2 but have no symptoms.
- **Mild Illness:** Individuals who have any of various signs and symptoms (e.g., fever, cough, sore throat, malaise, headache, myalgia, GI symptoms, anosmia, altered taste etc.) without dyspnea or abnormal imaging.
- **Moderate to Severe Illness:** Individuals who have respiratory frequency >30 breaths per minute, SpO2 ≤92% on room air at sea level, ratio of arterial partial pressure of oxygen to fraction of inspired oxygen (PaO2/FiO2) <300 and/ or lung infiltrates >50%.
- **Critical illness:** Individuals who have respiratory failure, septic shock and/or multi organ dysfunction.
- This guideline is applied for patients with moderate to Severe COVID cases – Oxygen saturation <92% in RA, RR >30/min, evident lung infiltrate or on invasive ventilatory support and/or High-risk group- Age >55 Y, comorbidities e.g. HTN, Type 2 DM, CKD, Chronic heart and lung disease etc.
- The regimen is applicable in acute medical ward, HDU or ICU setting.
- This document covers potential off-label and/or experimental/compassionate use of medications. There is no good evidenced based effective medications proven against SARS COV-2 at this stage. Any medications used must be at the discretion of the clinician treating the patient preferably as part of a clinical trial.
- Consensus is required between Internal Medicine, Respiratory medicine and ICU team.

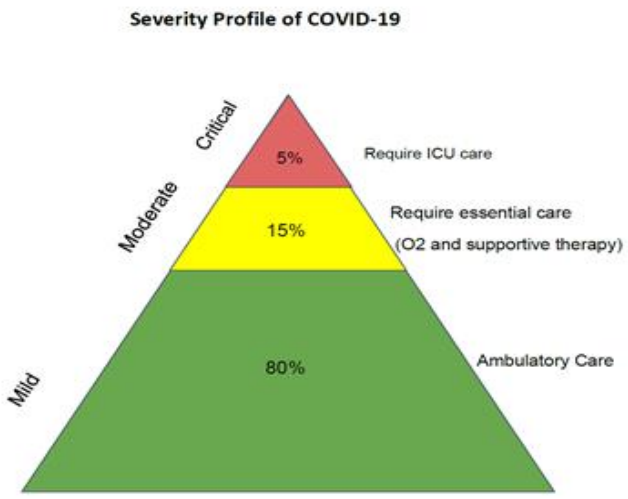


Figure 1: Severity profile of COVID19. Figure form Wu et al 2020[2]

<table>
<tr><th colspan="2">Laboratories for diagnosis, prognosis / risk stratification, and/or safety of agents Suggested for <u>all hospitalized</u> patients with confirmed or suspected COVID-19</th></tr>
<tr><td><u>Recommended daily labs</u>:
CBC with diff (trend total lymphocyte count)
Liver and renal function.</td><td><u>Viral serologies (if deranged LFT / anti-viral considered)</u>:
HBV serologies (sAb, cAb, and sAg)
HCV antibody, unless positive in past</td></tr>
<tr><td><u>For risk stratification (may be repeated q2-3 days if abnormal or with clinical deterioration)</u>:
D-dimer, Fibrinogen, APTT, PT
Ferritin / CRP
LDH
Troponin/ CPK
Baseline ECG (Monitor QTc)</td><td><u>If clinically indicated</u>:
• Routine blood cultures (2 sets)
• For acute kidney injury- send urinalysis and spot urine protein: creatinine
• Procalcitonin (if available)</td></tr>
<tr><td><u>Radiology</u>:
• Portable CXR at admission
• High threshold for PA/lateral in ambulatory patients, consider only if low suspicion for COVID-19 and result would change management.
Non-contrast CT is of limited utility in definitively diagnosing COVID-19 and should only be considered if it is likely to change management.</td><td><u>Respiratory workup with appropriate PPE</u>:
• Nasal SARS-CoV-2 PCR (Nose and throat), if not already performed. Tracheal aspirate if already intubated.
• Nasal viral PCR for influenza A, B and RSV test if available.
• As indicated, routine sputum for bacterial gram stain and culture, Legionella, Strep pneumonia urinary antigen.</td></tr>
</table>

COVID-19 Treatment Protocol

1.Supportive therapy – Hydration, antipyretics (Paracetamol), close monitoring of vitals including Oxygen saturation. For respiratory failure please follow **COVID-19 Acute Respiratory Care Pathway** as attached here**.**

2. Broad spectrum antibiotics should be considered for all cases with Lung infiltrates

According to the institute's antimicrobial guideline. The following is a suggestion:

- IV Ceftriaxone 2 gm daily or IV Meropenem 1 gm TDS plus oral Azithromycin or Doxycycline.
- Plus, IV Colistin and IV Vancomycin (If risk of MRSA infection) if on mechanical ventilation.

3.Hydroxychloroquine (HQ) and Lopinavir/Ritonavir (Anti-HIV drug) are not recommended. There is increased cardiotoxicity associated with HQ and increased mortality has been observed (HQ + Azithromycin) in recent observational studies.

4. Anti-Viral drugs :

A. Remdesivir 100 mg IV daily (200 mg on first day, then 100 mg daily) for 10 days for severe cases. **Remdesivir 100 mg IV daily (200 mg on first day, then 100 mg daily) for total 5 days** can be considered for less severe cases. Nil mortality benefit but reduces time to recovery.

- ***Inclusion criteria*: Saturation less than 94% or requiring supplemental oxygen or on mechanical ventilation.**
- *Exclusion criteria*: Evidence of multi-organ failure, Pressor requirement to maintain blood pressure, ALT > 5xULN, creatinine clearance < 30 ml/min, on ECMO.
- *Adverse effects*: No available data. Deranged LFT, infusion-related reactions- low BP, nausea, vomiting, sweating, and shivering.

B. Favipiravir 1600 mg PO BD on Day 1 then 600 mg BD for total 10 days. This can be considered as a cost-effective alternative.

5. Biological Therapy: Tocilizumab (Anti-IL-6) 8mg/kg (Max dose 800 mg; infusion over an hour) . Repeat dose after 8-12 hours if deteriorating or no clinical improvement.

Indication:

- Bilateral lung infiltrates
- Needs supplemental oxygen to maintain saturation above 92% or PaO2 /FiO2 <300 mmHg, RR > 30/min
- Features suggestive of cytokine storm(hyperinflammation) including ferritin ≥ 500, CRP>50, LDH>250, Lymphocyte count <0.6, D-dimer >1000 ng/ml (at least 2 criteria fulfilled)

Patient requires baseline QuantiFERON gold, Hepatitis B serology (including cAb), Hepatitis C serology, baseline D-dimer, Troponin, CK

Adverse effects: Mild neutropenia, deranged LFTs.

Exclusion:

Active diverticulitis or oesophageal perforation
LFT 5x times of the reference range
Current TB, bacterial or fungal infection not being treated

6. Anticoagulation: We strongly recommend each individual should be on DVT Prophylaxis (LMWH 40 mg SC daily or Heparin 5000 units SC BD) until there is any contraindication. COVID-19 can lead to hypercoagulable state due to systemic hyperinflammation and direct viral endothelial injury. D-dimers and DIC screening (INR, APTT, Fibrinogen) should be routinely checked. We suggest to be vigilant for venous thromboembolism (DVT/PE) and consider **for therapeutic anticoagulation** if there is evident clinical or biochemical (High level of D-dimer >1,000-2,000 ng/ml) suspicion. There is post discharge 4-6 weeks of oral anticoagulation (Rivaroxaban 10 mg daily) or prophylactic LMWH also suggested in high risk cohort.

7. **Convalescent Plasma therapy (CPT)**: This has shown some efficacy in COVID cases on mechanical ventilation or ECMO in observational data.

Indication: Severe or immediately life-threatening COVID-19

1. Age >18 years old
2. Positive SARS-CoV-2
3. Admitted in ICU
4. Informed consent
5. Severe or life-threatening disease defined by at least one of the following:
- Increasing dyspnea
- Respiratory rate >30
- SpO2 <88%
- P/F ratio <300
- Lung infiltrate >50% within 24-48 hours
- Septic shock
- Multi organ failure

Donor Eligibility:

1. Evidence of COVID-19 by a laboratory test either nasopharyngeal positive PCR test or a positive serological test for SARS-CoV-2 antibodies after recovery.
2. Complete resolution of symptoms at least 14 days before the donation. A negative result for COVID-19 by a diagnostic test is not necessary to qualify the donor.
3. A neutralizing antibody titre of at least 1:160. A titre of 1:80 may be considered acceptable if an alternative matched unit is not available.

Dosage: 200 ml of plasma infusion over an hour should be given and can be repeated in 12 hrs for critical patients. Be vigilant for transfusion induced reaction.

8. Systemic steroids: Systemic steroids should be avoided in early viremic phase and in mild COVID cases given potential harm. Steroids can be considered in severe/critical COVID cases requiring oxygen or ventilatory support (RECOVERY Trial) , refractory septic shock, severe ARDS and evident cytokine storm (in addition to Tocilizumab). Methylprednisone 1-2 mg/kg BD or oral Dexamethasone 10 mg BD for 5-7 days.

9. A single dose of Ivermectin (anti-parasitic drug) showed viral clearance in 48 hours in laboratory setting. There is some weak human study **(Not recommended at this stage)**.

10. Currently there are no data to support either starting or stopping ACEi/ARBs on any patients with COVID-19.

11. There are reports of NSAID use preceding clinical deterioration in some patients with severe COVID-19 disease. We recommend to avoid prescribing NSAIDs while patients are admitted.

COVID-19 Acute Respiratory Care Pathway

1. **Supplemental oxygen** (Nasal prongs/ Face Mask/ Face mask with reservoir bag) therapy to maintain oxygen saturation at 92%-96% *(Figure 1,2)*.

2. **High flow nasal cannula (HFNC) therapy:** HFNC therapy can be used for hypoxia associated with COVID-19 disease, provided good nasal progs fitting and staff wearing optimal airborne PPE and preferably should be done in a single / negative pressure room.

3. **Non-invasive ventilation (NIV)/CPAP:** Non-invasive ventilation therapy is an aerosol generating procedure and should be performed preferably in a negative pressure room or single room with staff maintaining strict airborne PPE precaution with a non-vented mask.
   CPAP can be considered as an escalation from HFNO in early ARDS phase and in a center where invasive ventilation facility or skilled manpower not available or as a bridging therapy to emergent intubation. NIV is also to be considered in COVID-19 cases overlapped with Cardiac failure or Obesity hypoventilation syndrome (CPAP) or COPD (BiPAP). We should also keep in mind that historical data (in MERS, SARS and Classic ARDS) showed high failure rate of NIV, delayed intubation and increased mortality.

4. The starting CPAP pressure could be 8-10 cmH_2O pressure and an FiO2 of 0.6 and should be titrated to maintain the target saturation 92-96% or 88-92% in COPD. The CPAP can be increased up to 12-15 cmH_2O with FiO2 of 1.0 (entrained oxygen via side port) (*Figure 3*).

5. The ideal BiPAP settings probably involve using a high level of end-expiratory pressure (EPAP) with a low driving pressure/ pressure support (e.g., 12-16 cm of IPAP with 8-10 cm EPAP) to avoid ventilator induced lung injury.

6. **Non-invasive ventilation** (single limb) (*Figure 3*) machine should be converted to a NIV with **Non-vented mask** plus exhalation port plus antimicrobial filter *(Figure 3,4*) to mitigate the aerosolization risk and should be preferably delivered in a single / negative pressure room strictly with full PPE. The other option would be to use the standard dual limb invasive ventilatory machine with Non-vented mask as a NIV therapy if endotracheal intubation is not an option for the given case or cannot be offered due to staffing / local expertise issue.

7. **Helmet Mask** (*Figure 5*): Helmet mask reduces the risk of aerosolization and a highly compliant device to facilitate higher PEEP without increased mask leak issue. However, the availability of this mask would be very limited.

8. **Awake pronation:** While proning has been used with good result in patient with severe ARDS but recent anecdotal reports showed benefit in conscious non-intubated patient. Prone position facilitates the lung recruitment and improved ventilation - perfusion matching. Preferably patient should be in prone position for 12-16 hrs./day. however, even intermittent 30 minutes to 2 hrs. prone position would be beneficial. If patient cannot tolerate full pronation, lateral prone position can be considered.

A major advantage of prone positioning is that it can be combined with a variety of additional techniques:

- Prone positioning + room air
- Prone positioning + low-flow nasal cannula
- Prone positioning + HFNC (Increased risk of cannula displacement)
- Prone positioning + BiPAP/CPAP via a facial mask (Increased risk of mask leak)

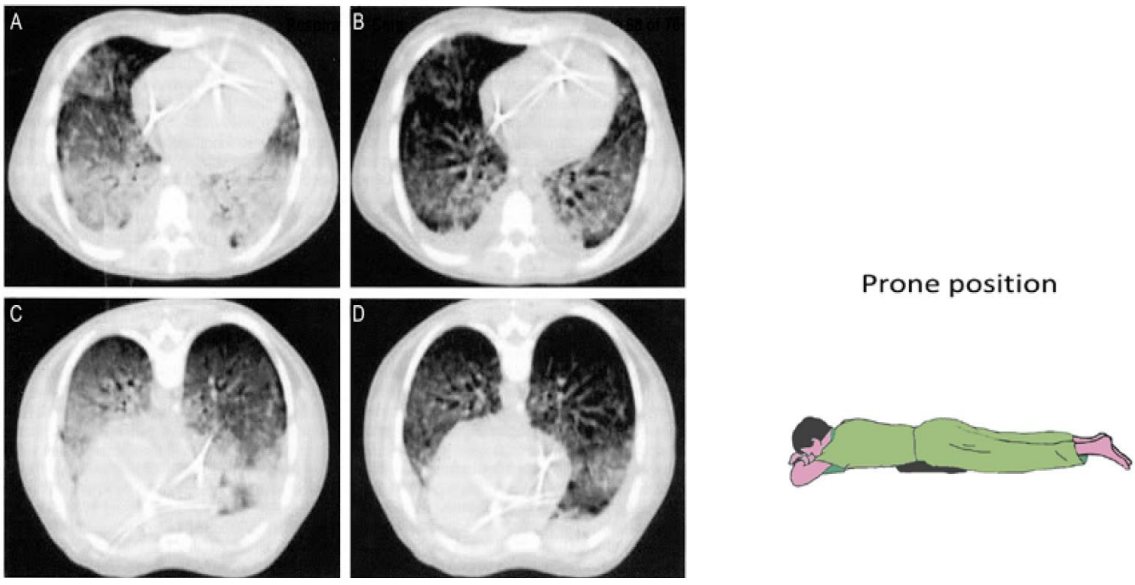


*Figure 6: Effects on lung densities of supine positioning at **A)** end-expiration and at **B)** end-inspiration, and prone positioning at **C)** end-expiration and **D)** end-inspiration (ERS,1969)*

Oxygen Delivery Algorithm

(WHO IMAI Clinician Manual, Volume 1 WHO 2011)

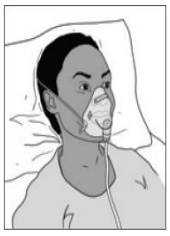
Place prongs inside the nostril. Hook tubing behind ears. Flow rates higher than 5-6 L will dry mucous membranes.

- Start oxygen at 2-6 L/min
- Use nasal prongs
- Assess response

If increasing respiratory distress or SpO_2 < 90% (88% in COPD)

Estimated FiO2 on different oxygen device

- 2-6 L/min - FiO2 28-40%
- 6-10 L/min - FiO2 40-60%
- 10-15 L/min-FiO2 60-95%



Secure mask firmly on face over nose and mouth. Pull strap over head.

- Use face mask
- **Increase oxygen to 6-10 L/min**
- Assess response

If increasing respiratory distress or SpO_2 <90% (<88% in COPD)

Make sure bag is full to deliver highest oxygen concentration. An empty bag is dangerous.

- Use face mask with reservoir
- **Increase oxygen to 10-15 L/min**
- Make sure bag inflates
- Call for help
- Assess response

If increasing respiratory distress or SpO2 <90% (<88% in COPD)

Transfer to a hospital with available invasive mechanical ventilator possible

- Call for help for possible endo-tracheal intubation
- Start manual ventilation (Bag and mask with good fit) with high-oxygen flow
- Alternatively, HFNO if available and intubation not appropriate or not available.

Figure 1: Step wise escalation of supplemental oxygen delivery algorithm

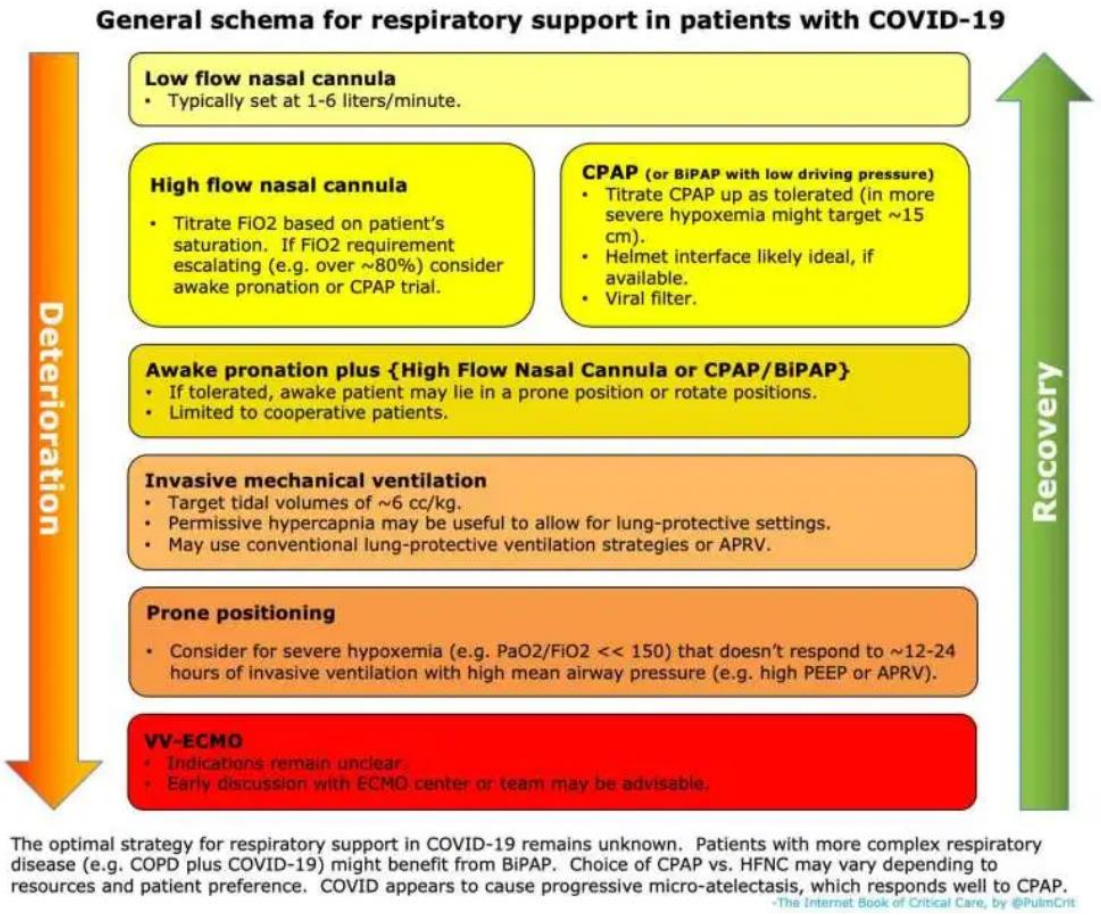


Figure 2: Algorithm of Acute respiratory failure management

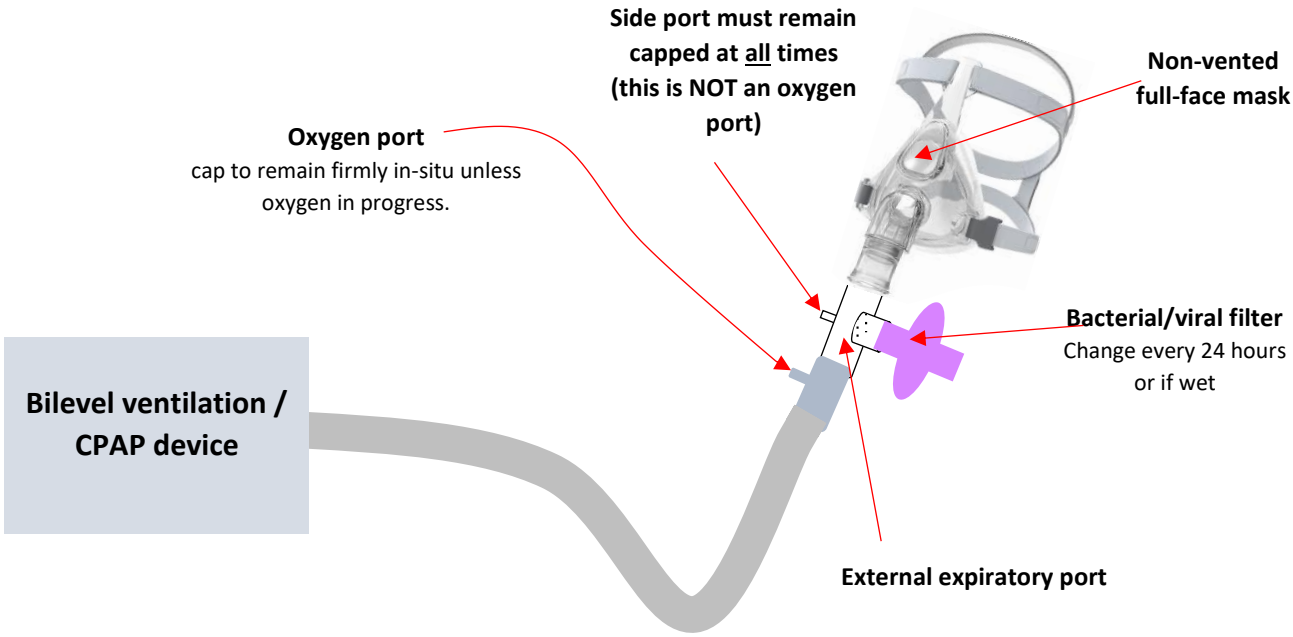


Figure 3: Single Limb NIV with non-vented mask, expiratory and oxygen port and filter

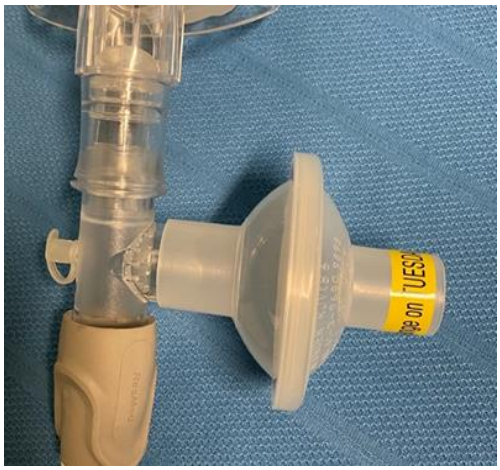


Figure 4: Antimicrobial Filter

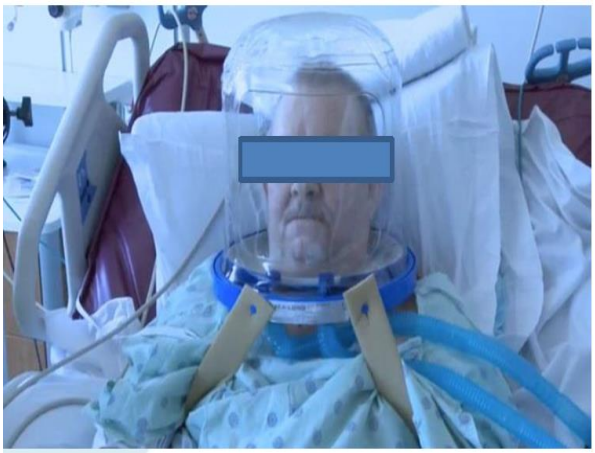


Figure 5: Helmet Mask

9. **Mechanical ventilation (MV):** High mortality has been globally experienced on MV and would be a concern for Bangladesh due to lack of clinical expertise, ICU trained nursing support and ventilation related complications.

   Indication: Clinical judgment on the basis of the following parameters:

- Signs of respiratory distress (e.g., accessory muscle use; paradoxical abdominal breathing)
- Rapid progression of disease.
- SpO2 sat <90% despite maximal supplemental oxygen.
- Arterial pH <7.3 with PaCO2 >50.
- Patient requiring >40 L/minute HFNO and FiO2 >0.6.
- Hemodynamic instability; multiorgan failure.

   Lung protective mechanical ventilation (MV) is recommended for management for acute respiratory failure - Low tidal volume strategy (4-8 ml/kg predicted body weight) and limiting plateau pressures < 30 cmH2O. Permissive hypercapnia is usually well tolerated and may reduce volutrauma. Airway pressure release ventilation can be trialed for optimal lung recruitment; Not very effective in obstructive airway disease (Asthma, COPD).

10. **Prone positioning:** Suggest prone ventilation if the low tidal volume ventilation fails e.g. PaO2/FiO2 [P/F] ratio <150 mmHg or worsening oxygenation after intubation. This should be done in the context of a hospital guideline (Preferably 12-16 hrs/day) that includes suitable PPE for staff, and that minimises the risk of adverse events, e.g. accidental extubation.

11. **For patients who fail prone ventilation** (e.g. P/F ratio <150 mmHg while prone), may consider the following interventions:

- Lung recruitment maneuvers and high positive end expiratory pressure (PEEP) strategies as follows:

Principle for FiO2 and PEEP adjustment

FiO2	0.3	0.4	0.5	0.6	0.7	0.8	0.9	1.0
PEEP	**5**	**5-10**	**10-18**	**18**	**18**	**18**	**18**	**18-24**

- Neuromuscular blockade for patients with refractory hypoxemia (eg, P/F <100 mmHg) or ventilator dys-synchrony.

- Trial of inhaled pulmonary vasodilators such as Nitric Oxide or Prostacyclin e.g. epoprostenol/Iloprost (data lacking, increased risk of aerosolization, should not be administered unless a specific protocol and experienced staff are in place).

- ECMO as a last resort; however, ECMO is not universally available.

12. **Fluid management:** A conservative fluid management strategy is recommended until evident tissue hypoperfusion. Where possible avoid 'maintenance' intravenous fluids, high volume enteral nutrition, and fluid bolus for hypotension.

13. **Suctioning:** Closed inline suction catheters are recommended. Any disconnection of the patient from the ventilator should be avoided to prevent lung decruitment and aerosolization. If necessary, the endotracheal tube should be clamped and the ventilator disabled (to prevent aerosolization).

14. **Nebulisation:** Use of nebulisers is not recommended and use of metered dose inhalers are preferred where possible.

15. **Bronchoscopy:** Diagnostic bronchoscopy is not recommended. It is not necessary for the diagnosis of viral pneumonia and should be avoided to minimise risk of aerosolization. Tracheal aspirate samples for diagnosis of COVD-19 are sufficient and Bronchio-alveolar lavage (BAL) is not usually necessary.

16. **Extubation from mechanical ventilation:** Standard weaning protocols should be followed. HFNO and/or NIV (well fitted facemask with separate inspiratory and expiratory limbs) can be considered as bridging therapy post-extubation but must be provided with strict airborne PPE.

17. **Tracheostomy:** This represents an aerosolizing procedure and must be considered in clinical decision making. Optimal PPE should be utilized at all times.

Summary of COVID-19 Management

- **Management of Moderate to severe & mild with comorbidity of COVID 19 patients in BD Settings:**

1. **HQ alone or HQ + Azith / Lopinavir + Ritonavir are not recommended except for trial.**

2. **Respiratory Failure:**
   - Supplemental oxygen with nasal prongs / full face mask/ NRB mask to maintain saturation 92-96% (88-92% in COPD).
   - We recommend intermittent awake prone positioning to improve VQ mismatching.
   - HFNC and CPAP therapy in a safe clinical environment should be considered prior to mechanical ventilation.

3. Broad spectrum Antibiotics from Pneumonic stage
   - Dose: Inj Ceftriaxone 2 gm daily/ Inj Meropenem 1 gm tds plus atypical pneumonia cover with Azithromycin or Doxycycline.

4. Remdesivir can be used in viraemia phase. No mortality benefit but it can reduce time to recovery! No difference between 5 days vs 10 days course.
   - Dose: IV 200 mg on day 1 then 100 mg daily total 5- 10 days course.

Alternative is Favipiravir 1600 mg PO bid on day 1 then 600mg bid for total 10 days.

5. Tocilizumab is advised to use even at early stage! If features of cytokine storm (at least 2 of these criteria- CRP>50, Ferritin> 500, LDH>250, Lymphocyte<600, D-Dimer>1000)
   - Dose: 8mg/kg IV (Max 800 mg) over 1 hour, can be repeated after 12 hours.

6. Prophylactic anticoagulation for all hospitalized patients. Therapeutic Anticoagulation in clinically or biochemically (high D-dimer) suspected thrombosis.
   - Prophylactic LMWH dose- 40 mg SC daily
   - Therapeutic LMWH: 1 mg/kg per dose 12 hourly (If normal renal function)

7. Steroid can be used in severe COVID, refractory shock, ARDS and cytokine storm.
   - Dose: Methylprednisone 1-2 mg/kg BD; or Dexamethasone 10 mg BD.

8. Convalescent Plasma therapy - For Severe or Mechanically ventilated patients. Antibody titre should be checked before institution.
   - Dose: 200 ml infusion over one hour, can be repeated after 12 hours.

- **For asymptomatic and mild cases without any comorbidity no specific Rx is required.**

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