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COVID-19 Pandemic and The Anesthesiologist







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CHAPTER 3

Management Guidelines

Nitin Sethi, Mahindra Singh Baansal

"Planning is the Essence of Good Management."

–Lisa Murkowski

Ever since the COVID-19 epidemic struck the world in late 2019, a plethora of clinical management guidelines has been published by various government agencies and academic societies. A brief overview of some of these important guidelines is presented which are:

1. World Health Organization: Living Guideline
2. COVID-19 Treatment Guidelines by National Institutes of Health
3. Ministry of Health and Family Welfare Clinical Management Protocol

WORLD HEALTH ORGANIZATION: LIVING GUIDELINE

The living guideline[1] is the updated evidence-based recommendation regarding various drugs used for COVID-19 treatment. The current guideline is the 6th version.

As per WHO COVID-19 severity[2] is categorized as:

- *Critical COVID-19:* Acute respiratory distress syndrome (ARDS), sepsis and septic shock as per specified criteria requiring the use of life-saving critical care measures.
- *Severe COVID-19:* Defined as room air oxygen saturation (SpO_2) <90% with signs of severe respiratory distress.
- *Non-severe COVID-19:* No signs of critical or severe COVID-19.

Recommendations as per the living guidelines are as follows:

- Combination of neutralizing monoclonal antibodies[3] casirivimab (REGN 10933) and imdevimab (REGN 10987) that can bind to SARS-CoV-2 spike protein can be suggested for treatment with patients with non-severe COVID-19. It may likely reduce hospitalization risk and symptom duration. This recommendation does not apply to children.
- In seronegative severe or critical COVID-19 patients, casirivimab-imdevimab can be used. Its use is likely to reduce mortality and the need for mechanical ventilation in these patients.
- Patients with severe and critical COVID-19 should receive both corticosteroids and IL-6 receptor blockers (tocilizumab and sarilumab)

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should be administered in patients with severe and critical COVID-19 patients.[4] There are suggestions without direct evidence that IL-6 receptor blockers should be used in patients not responding to corticosteroids treatment and without any multi-organ failure. Sarilumab is not indicated for use in children.

- There is no recommendations for use of Ivermectin[5] use in COVID-19 except in a clinical trial scenario.
- There is a strong recommendation against the use of hydroxychloroquine or chloroquine[6] for COVID-19 treatments. Also, there is no effect of the addition of azithromycin to hydroxychloroquine to disease outcome.
- There is no evidence that the use of lopinavir/ritonavir[7] has any impact on the clinical outcome of the patient and its use is therefore not recommended.
- Remdesivir[8] use for COVID-19 treatment is not recommended irrespective of the disease severity. As there is no evidence that its use impacts clinical outcomes or reduces mortality.
- There is a strong recommendation for systemic corticosteroids (dexamethasone, prednisolone) administration[9] in patients with severe and critical COVID-19. When administrated for up to 7–10 days, there is no increased risk of adverse events with the use of steroids. The use of steroids significantly reduces 28-day mortality and the need for mechanical ventilation. In patients with non-severe COVID-19, use of corticosteroids is, however, not recommended.

COVID-19 TREATMENT GUIDELINES BY NATIONAL INSTITUTES OF HEALTH

Testing for COVID-19 Infection

- For diagnosis of acute COVID-19 infection use of nucleic acid amplification test (NAAT) with sample collected using a nasopharyngeal or oropharyngeal swab is recommended. In suspected COVID-19 patients on mechanical ventilation with an initial negative test on the upper respiratory tract sample, obtaining endotracheal aspiration is recommended. In asymptomatic person within 90 days of a prior COVID-19 infection, NAAT need not be repeated. However, patients recover from a previous infection but present with symptoms consistent with COVID-19 infection a NAAT should be considered. Serological testing is only indicated to assess the person's immune response and not for sole diagnosis of COVID-19 infection.[10,11]
- Use of any drug for pre-exposure and post-exposure prophylaxis (PEP) to COVID-19 infection is not recommended except in a clinical trial scenario. [12]

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- As per NIH guidelines, COVID-19 severity is categorized as:[10]
  - *Mild illness:* Patients may present with various signs and symptoms such as fever, malaise, anosmia, vomiting, sore throat, diarrhea. There is no dyspnea or any radiological abnormality.
  - *Moderate illness:* Presence of lower respiratory tract disease on clinical assessment and radiology evaluation with SpO_2 ≥94% on room air.
  - *Severe illness*: Patients with room air SpO_2 <94%, a respiratory rate >30/min, PaO_2/FiO_2 >300 mm Hg or lung infiltration >50%.
  - *Critical illness*: Patients present with clinical features of acute respiratory distress syndrome, septic shock and exaggerated inflammatory response.

General Management of Non-Hospitalized with Acute COVID-19

- In non-hospitalized COVID-19 patients, supportive care with steps to reduce COVID-19 transmission risk should be initiated and patients should be advised when to contact a healthcare provider.
- Telemedical consultation before receiving in-person care should be encouraged. Medical care should be planned based on patient's clinical signs and symptoms and disease progression.[13]

Management of Non-Hospitalized COVID-19 Adults[10]

- The use of chloroquine or hydroxychloroquine, azithromycin, doxycycline, lopinavir/ritonavir or any other HIV protease inhibitor is not recommended.
- Anticoagulant and antiplatelet drugs for the prevention of vascular thrombosis are not recommended until there is a specific indication.
- The use of dexamethasone or any other systemic glucocorticoid is not recommended in the coherence of any other indication.
- In patients after hospital discharge in stable condition or those requiring supplemental oxygen continued use of remdesivir, dexamethasone and baricitinib are not recommended.
- If the patient is discharged from the emergency department due to lack of inpatient care facility but needs supplemental oxygen, then dexamethasone 6 mg PO once daily can be used but should not exceed 10 days. Evidence for or against the use of remdesivir is insufficient. No recommendation for use of baricitinib except in a clinical trial setting.
- Any of the combinations of anti-SARS-CoV-2 spike protein monoclonal antibody (*see section: recommendations for use of monoclonal antibodies*).

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Management of Hospitalized COVID-19 Adult Patients[10]

- The use of dexamethasone or any other corticosteroids is not recommended, if the patient does not need supplemental oxygen therapy.
- For patients requiring minimal supplemental oxygen, use of remdesivir is recommended. A combination of dexamethasone and remdesivir can be used for patients with increasing supplemental oxygen requirements. Dexamethasone alone should be used if remdesivir combination cannot be used or is unavailable.
- Patients in need of high flow oxygen delivery or non-invasive ventilation either dexamethasone alone or in combination with remdesivir can be used. Baricitinib or IV tocilizumab can also be added to the treatment regimen. Tocilizumab can be used if baricitinib is not available and IV sarilumabif tocilizumab is unavailable.
- Dexamethasone plus IV tocilizumab should be administered within 24 hours of admission in patients needing invasive mechanical ventilation or ECMO. Sarilumab to be used during tocilizumab unavailability.
- Remdesivir is administered 200 mg IV once followed by 100 mg IV once a day for 4 days. If there is no clinical improvement till day 5 treatment can be extended up to 10 days.[14]
- Dexamethasone is administered 6 mg IV or PO once daily for 10 days or until hospital discharge.[14]
- Baricitinib is given 4 mg once a day until 14 days or up to hospital discharge.[15]
- Tofacitinib is given 10 mg twice daily until 14 days or up to hospital discharge.
- Tocilizumab dose is administered as a single IV dose of 8 mg/kg actual body weight (up to 800 mg).[16]
- Sarilumab is administered as 400 mg IV infusion over one hour or as a subcutaneous injection using a pre-filled syringe.

Care of the Critically Ill Adult Patient with COVID-19[10,17,18]

Infection Control

- N-95 respirator should be used by healthcare workers while performing aerosol-generating procedures in addition to other personal protective equipment.
- A negative pressure room should be utilized while performing any aerosols generating procedures.
- Endotracheal intubation in COVID-19 patients should be performed by healthcare workers having expertise in airway management and video laryngoscope should be used if possible.

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Hemodynamics

- Dynamic parameters such as temperature, capillary refill time and lactate level should be preferred over static parameters to assess fluid responsiveness.
- Fluid resuscitation should be done using buffered crystalloid solutions. Use of hydroxyethyl starch for resuscitation in septic shock is not recommended. Also, albumin is not recommended as initial use for resuscitation.
- Norepinephrine should be the first choice vasopressor. Vasopressors should be titrated targeting a mean arterial pressure (MAP) ≥60–65 mm Hg. Additional drugs to be added to norepinephrine to raise MAP should be either vasopressin up to 0.03 U/min or epinephrine. Use of dopamine is not recommended for raised MAP or renal protection.
- In patients with persistent hypoperfusion and underlying cardiac dysfunction despite using all recommended treatment modalities, dobutamine can be used.
- Invasive arterial pressure monitoring is essential for all patients requiring vasopressor support.
- For patients with refractory septic shock low-dose corticosteroids therapy is recommended even if patients have completed their course of corticosteroids treatment for COVID-19 infection.

Oxygenation and Ventilation

- In type I respiratory failure patient's high flow nasal oxygen (HFNO) is preferred over non-invasive positive pressure ventilation (NIPPV).
- In patients with persistent hypoxemia despite increasing supplemental oxygen requirement a trial of awake proning should be considered to improve oxygenation.
- In patients who meet criteria for invasive mechanical ventilation use of awake proning is not recommended.
- The recommended ventilation settings for invasive mechanical ventilation are: tidal volume (V_t) 4–8 mL/kg predicted body weight and target plateau pressure <30 cmH_2O. A conservative fluid strategy is to be used and no recommendation for use of inhaled nitric oxide.
- High positive end-expiratory pressure (PEEP) strategy is preferred over low PEEP in mechanically ventilated moderate to severe hypoxemic patients. To facilitate ventilation use of either intermittent boluses of neuromuscular blocking drugs or continuous infusion.
- For patients with severe ARDS use of a recruitment maneuver is recommended. Incremental PEEP recruitment is not recommended. If no improvement is seen, then inhaled pulmonary vasodilation to be used as rescue therapy.

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Acute Kidney Injury Management

- In critically ill patients with acute kidney injury (AKI) who have indications for renal replacement therapy continuous renal replacement therapy (CRRT) is to be used.
- In absence of CRRT prolonged intermittent renal replacement therapy rather than intermittent hemodialysis to be used.

Antibiotic Therapy

Evidence for or against the use of empiric antibiotic therapy in absence of any indication is insufficient. The use of antibodies has to be assessed daily to avoid any adverse complications.

Extracorporeal Membrane Oxygenation (ECMO)

Evidence recommending for or against the use of ECMO in patients with refractory hypoxemia despite all prescribed treatment modalities is insufficient.

Antiviral Drugs[19]

- Currently, the only FDA approved drug for COVID-19 treatment is remdesivir.
- The recommendation for or against the use of ivermectin for COVID-19 treatment is insufficient.
- Use of chloroquine, hydroxychloroquine, azithromycin, lopinavir/ritonavir or other HIV-protease inhibition is not recommended.
- Nitazoxanide use is not recommended except in a clinical trial setting.

Recommendation for Use of Antibody Products

- Any of the three combinations of anti-SARS-CoV-2 spike protein monoclonal antibody regimens can be used in non-hospitalized mild-to-moderate COVID-19 patients:[20]
  1. Casirivimab 600 mg and imdevimab 600 mg combination IV or subcutaneous infusions
  2. Bamlanivimab 700 mg plus etesevimab 1400 mg IV infusion
  3. Sotrovimab 500 mg IV infusion
- If there is a shortage of monoclonal antibodies or logistic constraints to treatment administration, then priority has to be given to treatment of COVID-19 rather than post-exposure prophylaxis to COVID-19 infection. In addition, unvaccinated or partially vaccinated and vaccinated individuals who are not expected to have an adequate immune response should be prioritized for treatment.[10]

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- Unvaccinated, partially vaccinated or fully vaccinated individuals with the inadequate immune response with increased risk of progression to severe COVID-19 infection should be considered for PEP with casirivimab plus imdevimab. The dose for PEP is 600 mg casirivimab plus 600 mg imdevimab for subcutaneous injection at four different sites or as a single IV infusion (2.5 mL/injection). Evidence for recommendation for the use of monoclonal antibody PEP in children is insufficient.[21]
- The evidence for or against the use of high titer COVID-19 convalescent plasma for treatment of non-hospitalized COVID-19 patients or in COVID-19 patients with impaired immunity is insufficient. The use of convalescent plasma is not recommended in either non-ventilated or mechanically ventilated patients without impaired immunity. The only exception is being non-ventilated patients in a clinical trial scenario.[22]
- The use of anti-SARS-CoV-2 specific immunoglobulins is not recommended.

Cell-based Therapy and Immunomodulation Under Evaluation[10]

- Mesenchymal stem cells for COVID-19 treatments is not recommended.
- The use of baricitinib with dexamethasone, dexamethasone alone, tocilizumab with dexamethasone is as per disease severity as given in the section "*management of hospitalized adults with COVID-19*".
- Evidence in favor or against the use of Colchicine in non-hospitalized patients, granulocyte-macrophage colony-stimulating factor inhibition for hospitalized patients, inhaled budesonide, IL-1 inhibitors, interferon-beta for early mild-to-moderate COVID-19, sarilumab for patients within 24 hours of ICU admission and fluvoxamine is insufficient.
- Use of immunomodulation drugs such as baricitinib with tocalizumab, interferon (alpha/beta) in critically ill, bruton tyrosine kinase inhibitors (acalbrutinib, ibrutinib), Janus kinase inhibitor (JKI) (ruxolitinib, tofacitinib), non-SARS-CoV-2 specific IVIG (except for COVID-19 treatment complications), sarilumab for patients not requiring ICU care, and anti-IL-6 monoclonal antibody siltuximab is not recommended apart from clinical trial settings.
- Colchicine use in hospitalized COVID-19 patients is not recommended.

Antithrombotic Therapy[10, 23]

- Measurement of coagulation parameters such as D-dimer, prothrombin time, platelet count and fibrinogen is not recommended in non-hospitalized patients. Even in hospitalized patients, evidence for measurement is insufficient.

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- Patients with COVID-19 or chronic anticoagulation antiplatelet therapy should continue with these treatments.
- Anticoagulant or antiplatelet medication preventing vascular thrombosis is not indicated in non-hospitalized COVID-19 patients unless there are other indications or if in a clinical trial.
- Prophylactic anticoagulants should be given in hospitalized non-pregnant COVID-19 patients.
- Patients receiving venous thromboembolism (VTE) prophylaxis should not be discharged from the hospital consider VTE prophylaxis in at-risk patients having low bleeding.
- There is insufficient evidence for VTE screening in COVID-19 patients without signs or symptoms.
- Prophylactic anticoagulation in pregnant hospitalized COVID-19 patients is recommended unless contraindicated.

Supplements[10]

Evidence for use of vitamin C, vitamin D or zinc for COVID-19 treatment is insufficient.

Concomitant Medications[10]

- Patients with COVID-19 receiving concomitant medications such as ACE inhibitors, systemic or inhaled corticosteroids, NSAIDs, antacids should continue with these medications unless otherwise indicated.
- The use of off-label medications to treat COVID-19 is not recommended until or unless their safety and efficacy has been demonstrated in COVID-19 patients accept in a clinical trial scenario.

COVID-19 and Special Populations

Pregnant Patients[24]

- Hospitalization of COVID-19 pregnant patients should be done in a facility with facilities equipped for maternal and fetal care.
- Potentially effective treatment of COVID-19 as per treatment guidelines should not be withheld from pregnant women.
- Obstetric indication and not maternal diagnosis of COVID-19 should determine the timing of delivery.
- Breastfeeding is not contraindicated for pregnant patients with a confirmed diagnosis of COVID-19.

Children[25]

- Supportive care is sufficient for most children with mild or moderate disease.

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- In hospitalized COVID-19 children ≥12 years with underlying risk factors (neurological impairment, genetic syndromes, obesity, immunocompromised, cardiac disease) for severe disease and hospitalized children greater than 16 years who have increased need for oxygen therapy regardless of the risk factors, use of remdesivir is recommended.
- Dexamethasone is indicated for hospitalized COVID-19 children in need of high flow oxygen, non-invasive/invasive ventilation or ECMO.
- Recommendation for or against the use of anti-SARS-CoV-2 monoclonal antibodies for non-hospitalized COVID-19 children with risk factors for severe disease is insufficient.
- Use of convalescent plasma is recommended only in non-ventilated hospitalized children recruited in a clinical trial.
- There evidence for or against the use of a combination of baricitinib and remdesivirin hospitalized children in whom corticosteroids are contraindicated.
- Tocilizumab use in hospitalized COVID-19 children or in children with multi-system inflammatory syndrome (MIS-C) is insufficient. Use of sarilumab is not recommended in children except in a clinical trial.

MINISTRY OF HEALTH AND FAMILY WELFARE (MoHFW) CLINICAL MANAGEMENT PROTOCOL

As per MoHFW guidelines, the clinical severity of COVID-19 is classified as:[26]

- *Mild disease:* Patients with mild symptoms such as fever, cough, sore throat, malaise, headaches and nasal congestion with no shortness of breath or oxygen desaturation.
- *Moderate disease:* Patient with pneumonia but no signs of severe disease. The presenting symptoms include fever, cough, hypoxia (SpO_2 90–93% on room air), respiratory rate ≥24/minute.
- *Severe disease:* Patients present with severe pneumonia or acute respiratory distress syndrome. Severe pneumonia is characterized by clinical signs of pneumonia with respiratory rate >30 breaths/min, severe respiratory distress, SpO_2 <90% on room air.

MANAGEMENT OF COVID-19[27]

- *Mild cases*: Patients with mild cases can be managed at home or COVID care center. Fluids should be taken to maintain hydration. Steam inhalation and warm water gargles should be performed by patients. Temperature and SpO_2 monitoring should be done at regular intervals. Fever should be controlled with paracetamol 650 mg four times a day. Additional medications that can be considered are ivermectin (200 μg/kg

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OD for 3–5 days) or hydroxychloroquine (400 mg BD on day 1st followed by 400 mg OD for next four days) inhalation budesonide (800 μg twice daily for 5–7 days). If symptoms persist beyond seven days (persistent fever, worsening cough), then systemic steroids can be administered in consultation with physician.

- *Moderate cases:* A target SpO_2 of 90–96% (82–92% in COPD patients) to be achieved. Consider O_2 administration by nasal prongs, face mask or non-rebreathing reservoir bags depending upon the severity of hypoxia. Encourage early self proning in awake non-intubated patients. Prophylactic dose of unfractionated heparin (UFH) or low molecular weight heparin (LMWH) is to be started. IV methylprednisolone 0.5–1 mg/kg or dexamethasone 0.1–0.2 mg/kg for 5–10 days to be considered as per patient clinical response. Unless there is clinical suspicion of bacterial infection antibiotics should not be prescribed. Serial chest X-rays are to be done. Consider HRCT-chest only if clinical worsening of the patient condition. CRP and D-dimer to be monitored 24–48 hourly. IL-6 levels are to be done only if clinical conditions worsen.
- *Severe cases:* Target SpO_2 ≥90% in non-pregnant adults and >92–96% in pregnant patients using O_2 at 5 L/min. If oxygen saturation worsens, then the use of non-invasive ventilation (NIV) or high flow nasal cannula (HFNC) is to be considered. If NIV is not tolerated or increased work of breathing, then invasive mechanical ventilation is to be considered. Administer injection methylprednisolone 1–2 mg/kg in two divided doses (or dexamethasone 0.2–0.4 mg/kg) for 5–10 days. A prophylactic dose of UFH or LMWH is to be administered. Serial X-ray chest to be done and HRCT-chest only in clinical condition worsening. CRP and D-dimer to be monitored 24–48 hourly. IL-6 to be done if clinical deterioration. Patients requiring invasive mechanical ventilation should be ventilated using the ARDS-net protocol: V_t 6 mL/kg, RR 15–35/min, PEEP 5–15 cmH_2O. In patients with moderate-to-severe ARDS a higher PEEP instead of lower PEEP is recommended. If an ECMO facility is available, it may be considered in patients with refractory hypoxemia not responding to protective lung ventilation.

INVESTIGATIONAL THERAPIES[27]

- *Remdesivir:* It should be used in patients within 10 days of symptoms onset with moderate-to-severe disease requiring supplemental oxygen in a hospital setting. The patient should not be pregnant and not have any underlying renal or hepatic dysfunction.
- *Tocilizumab*: To be used in patients within 24–48 hours of severe disease or ICU admission. The patient should have significantly raised

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inflammatory markers (CRP/IL-6) with no clinical improvement despite steroid therapy.

CONCLUSION

Clinical management guidelines are evidence-based protocols for providing optimal care for COVID-19 patients. Adherence to the above guidelines can result in favorable clinical outcomes for COVID-19 patients.

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COVID-19 Pandemic and The Anesthesiologist

Although this is not the first book on the COVID-19 pandemic, this book is likely to be the most comprehensive one on the subject. Whether it is a method of home isolation care or a method of intensive care management, saving lives is the ultimate goal. Psychological issues are another major area, the viral infection has affected the mental status of the caregivers as well as the general public. This book has also emphasized the importance of robust preventive measures and the means to prepare for such undesirable episodes in the future. This is a humane effort to make this book a thorough, clear, and practical summary of the disease.



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