COMMENTARY

COVID-19: Management

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Abstract

Coronavirus disease (COVID-19) has grasped the world including Pakistan. Clinical features of this disease are variable, ranging from asymptomatic to critical disease. In this unprecedented global war, the Pakistan Chest Society has written a guideline for quick review for the specialists providing care to suspected or confirmed patients. This review highlights the approach to a patient with COVID-19, including definition of the various syndromes of the disease, the abnormal laboratory parameters and outlines the therapeutic measures which are currently under investigation.

Keywords: COVID-19, Acute respiratory distress syndrome, Pneumonia, SARS-CoV-2.

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Introduction

Coronavirus disease 2019 (COVID-19), caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) was identified in December 2019 as the cause of a cluster of pneumonia cases in Wuhan, China, that was declared later a pandemic by the World Health Organization (WHO) in March 2020.[1] Clinical features (Table-1) of the illness are variable with some patients having asymptomatic infection while the spectrum of symptomatic infection may range from mild to critical disease.[1-3] Acute viral pneumonia which may evolve to acute respiratory distress syndrome (ARDS) is potentially a major concern for morbidity and mortality associated with COVID-19 besides other life-threatening complications like arrhythmias, acute cardiac injury, and shock.[2] No age is immune for severe illness, however critical disease predominantly occurs in elderly individuals, especially those with underlying medical comorbidities like diabetes mellitus, hypertension, ischaemic heart disease, malignancy, and chronic lung/renal disease.[1,2] Beside some of the clinical features associated with severe disease, there are some laboratory parameters of severity, related to disease progression[4] (Table-2).

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Table-1: Clinical syndromes associated with COVID-19.

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, dyspnoea, nasal congestion, or headache. Rarely, patients may also present with diarrhoea, nausea and vomiting.
Pneumonia	Pneumonia but no signs of severe pneumonia and no need for supplemental oxygen.
Severe Pneumonia	Fever or suspected respiratory infection, plus one of: respiratory rate > 30 breaths/minute; severe respiratory distress; or SpO_2 $\leq$93% on room air.
ARDS	**Onset:** within 1 week of a known clinical insult or new or worsening respiratory symptoms. **Chest imaging (radiograph, 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/oedema if no risk factor present. **Oxygenation impairment in adults:** ◆ Mild ARDS: 200 mmHg < PaO_2/FiO_2[a] $\leq$ 300 mmHg (with PEEP or CPAP $\geq$ 5 cmH_2O, or non-ventilated) ◆ Moderate ARDS: 100 mmHg < PaO_2/FiO_2 $\leq$ 200 mmHg (with PEEP $\geq$ 5 cmH2O, or non-ventilated) ◆ Severe ARDS: PaO_2/FiO_2 $\leq$ 100 mmHg (with PEEP $\geq$ 5 cmH_2O, or non-ventilated) ◆ When PaO_2 is not available, SpO_2/FiO_2 $\leq$ 315 suggests ARDS (including in non-ventilated patients).
Sepsis	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, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, or laboratory evidence of coagulopathy, thrombocytopaenia, acidosis, high lactate or hyperbilirubinaemia.
Septic shock	Persisting hypotension despite volume resuscitation, requiring vasopressors to maintain MAP $\geq$ 65 mmHg and serum lactate level > 2 mmol/L.

[a] If altitude is higher than 1000 m, then correction factor should be calculated as follows: PaO2/FiO2 x barometric pressure/760.

[b] The sequential organ failure assessment (SOFA) score ranges from 0 to 24 and includes points related to six organ systems: respiratory (hypoxemia defined by low PaO2/FiO2); 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).

ARDS = Acute respiratory distress syndrome; SpO2 = Oxygen saturation; PaO2/FiO2 = ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2); PEEP = Positive end-expiratory pressure; CPAP = Continuous positive airway pressure; MAP = Mean arterial pressure.

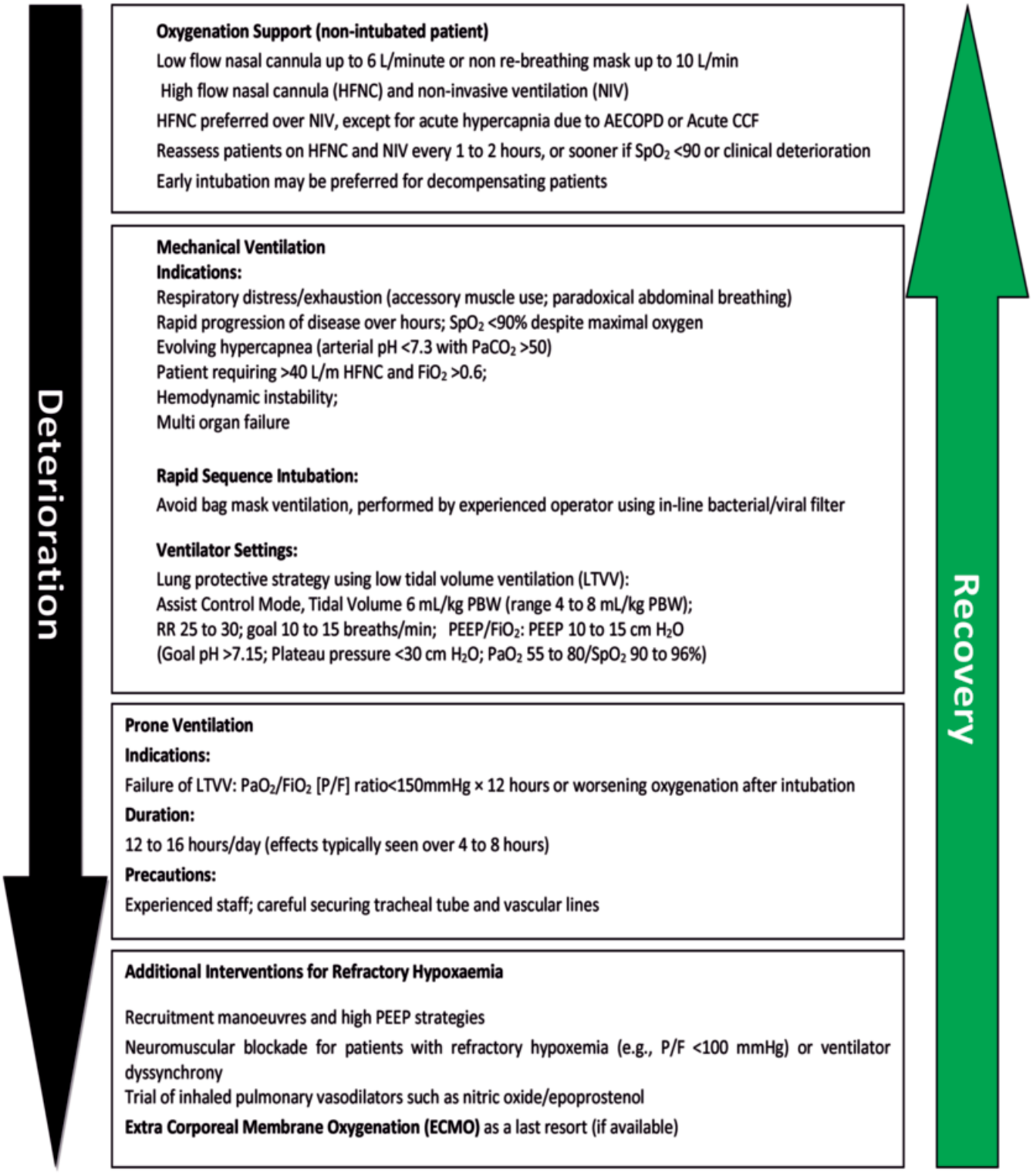

Figure: Respiratory support in patients with COVID-19 (Goal SpO2 90 to 96%).

Precautions: N95 mask, gown, gloves, eye protection; disposable stethoscope; negative pressure room for aerosol-generating procedures
AECOPD = acute exacerbation of chronic obstructive pulmonary disease; CCF = Congestive cardiac failure; SpO2 = oxygen saturation; PaCO2 = partial pressure of carbon dioxide; PaO2/FiO2 = ratio of arterial oxygen partial pressure (PaO2 in mmHg) to fractional inspired oxygen (FiO2); PEEP = Positive end-expiratory pressure;

Table-2: Laboratory features associated with severe COVID-19.

Abnormal Laboratory Parameter	Possible threshold
Lymphopenia: Absolute lymphocyte count	<800/micro L (normal range for age ≥21 years: 1800 to 7700/micro L)
D-dimer	>1000 n g /m L (normal range: <500 n g/m L)
CRP	>100 mg/L (normal range: <8.0 mg/L)
LDH	>245 units/L (normal range: 110 to 210 units/L)
CPK	>2× the upper limit of normal (normal range for troponin T high sensitivity: females 0 to 9 n g/L; males 0 to 14 n g/L)
Ferritin	>500 mcg/L (normal range: females 10 to 200 mcg/L; males 30 to 300 mcg/L)
Troponin	>2× the upper limit of normal (normal range: 40 to 150 units/L)

CRP: C-reactive protein; LDH: lactate dehydrogenase; CPK: creatine phosphokinase.

Approach to a Patient with COVID-19

The first step in the management of COVID-19 is to define the severity of disease (Tables 1 and 2). Subjects with non-severe disease do not require hospitalisation and can be managed at home/hospital or non-hospital based isolation facility using supportive care only (e.g. acetaminophen for pyrexia), close monitoring for clinical worsening and strict isolation precautions.[5] The onset of dyspnoea may raise concern for underlying pneumonia (moderate severity disease), and these patients often warrant hospitalisation. Patients with infiltrates on chest imaging but not requiring oxygen inhalation can still be considered to have moderate disease. The presence of any of the following features indicates severe disease: hypoxia (oxygen saturation (SpO_2) ≤93 percent on room air, or ratio of arterial oxygen partial pressure (PaO_2 in mmHg) to fractional inspired oxygen (FiO_2) (PaO_2/FiO_2) <300 mmHg),

Table-3: Therapeutic management of severe COVID-19.

Drug/agent	Recommendations
Hydroxychloroquine	Emergency use authorization by FDA Can prolong the QT interval (should be monitored) Dose: Oral: 400 mg twice daily on day 1, followed by 400 mg/day as a single dose or in 2 divided doses, for a total treatment duration of 5 days or 800 mg once on day 1, followed by 400 mg/day as a single dose or in 2 divided doses, for a total treatment duration of 4 to 7 days
Chloroquine	Emergency use authorization by FDA Can prolong the QT interval (should be monitored) Dose: ≥50 kg: Oral: 1 g (600 mg base) once on day 1 followed by 500 mg (300 mg base) once daily for a total treatment duration of 4 to 7 days (FDA 2020).
Azithromycin with hydroxychloroquine	Azithromycin 500 mg on day 1 plus 250 mg daily on days 2-5 (may be administered intravenously per clinician preference) ClinicalTrials.gov Identifier: NCT04329572 Both azithromycin and hydroxychloroquine are associated with QTc prolongation, and combined use may potentiate this adverse effect
Remdesivir	Novel nucleotide analogue, parenteral agent Activity against SARS-CoV-2 in vitro and in animal studies 200 mg as a single dose on day 1, followed by 100 mg once daily for a total duration of 5 to 10 days (Gilead 2020; NIH 2020a; NIH 2020b; NIH 2020c).
Convalescent plasma	Emergency use authorization by FDA Logistical challenges in finding appropriate donors and establishing testing to confirm neutralizing activity of plasma
Hyperimmune globulin	FDA emergency approval facilitating the therapeutic evaluation
IL-6 pathway inhibitors	China's National Health Commission guidelines include tocilizumab for severe COVID-19 associated with raised IL-6 levels
Lopinavir-ritonavir	Anti-HIV drug Demonstrated in vitro activity against the SARS-CoV No clear benefit of use in COVID-19 Dose: (400/100 mg) twice daily for 14 days Still under evaluation
Combination remdesivir, hydroxychloroquine/chloroquine, and lopinavir-ritonavir with and without interferon beta	Under trial by WHO (SOLIDARITY 2020)

FDA = Food and Drug Administration; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2; IL-6 =Interleukin 6.

respiratory rate >30/minute or respiratory distress and/or more than 50 percent involvement of the lung parenchyma on chest imaging.[2] Patients having laboratory abnormalities (Table-2) associated with disease progression should also be categorised similar to patients who have severe disease.[1,2]

Management of Severe COVID-19

Standard therapy (Table-3) for COVID-19 is unknown in hospitalised patients with severe or critical disease. According to the available data of those infected with SARS-CoV-2, up to 20 percent develop severe disease requiring hospitalisation with up to one-quarter requiring ICU admission (5-8% of total infected).[2] There are no well-controlled data supporting the use of any of the potential agents currently in use/under trials for managing severe COVID-19 disease.[6] For patients hospitalised with suspected or confirmed severe/life-threatening COVID-19 or those with laboratory risk factors for disease progression, agents currently recommended by experts include chloroquine or hydroxychloroquine with or without azithromycin, remdesivir, convalescent plasma (FDA's investigational new drug application), or other agents.[7,8] Interleukin-6 (IL-6) inhibitors (tocilizumab, sarilumab and siltuximab) improve outcomes in some of COVID-19 patients with life-threatening disease having features consistent with a cytokine release syndrome (elevated IL-6 levels, persistent pyrexia, and elevated CRP, procalcitonin, ferritin, and D-dimer levels).[9]

Supportive therapy includes but is not limited to management of hypoxaemia (Figure), placement of central venous line, arterial line if frequent ABGs monitoring anticipated for ventilated patients with ARDS, conservative use of IV fluids (>30 mL/kg) unless patients have sepsis or volume depletion from gastrointestinal losses or high fever, vasopressors (e.g. dopamine), antipyretics (acetaminophen is preferred over NSAIDs), and nutritional support. Nebulizer treatment is best avoided unless in isolation room for some patients with asthma or chronic obstructive pulmonary disease (COPD) exacerbation (risk of airborne infection caused by aerosol generation) where inhalers are preferred.[1,3,10] Empiric antibiotics (community-acquired or healthcare-associated pneumonia coverage) should be used only for suspected bacterial co-infection.[3] Systemic glucocorticoids are generally not advised for COVID-19 infection, unless needed for other indication (e.g., adrenal insufficiency, asthma, COPD).[11]

Differentiating COVID-19 from similar respiratory illnesses is important as the approach to management varies according to the underlying diagnosis. Patients with COVID-19 having mild upper respiratory symptoms cannot be differentiated from similar respiratory disease caused by common cold viruses like rhinovirus, adenovirus, enterovirus and other coronaviruses etc.[4] Viruses with marked seasonal variation, such as influenza and parainfluenza, typically cause more systemic symptoms than other cold viruses; however, they can rarely also cause illnesses similar to the common cold and are also among the differential diagnosis of mild COVID-19.[1] However patients with COVID-19 typically have high grade fever (99%) while rhinorrhoea, sore throat and headache may be less prominent as compared to patients with influenza.[4] Without considering specific laboratory testing (polymerase chain reaction, serology if needed), it is difficult to differentiate mild COVID-19 from these illnesses.

Patients with chronic respiratory diseases like allergic rhinitis, chronic bronchitis and bronchial asthma have history of long standing symptoms which may be associated with seasonal variations. If these patients develop COVID-19 infection, they may notice worsening of their respiratory symptoms but again require microbiological testing for confirmation of diagnosis.

In early or mild COVID-19 pneumonia, chest radiograph may be normal and pulmonary involvement is typically increased over the course of illness (bilateral consolidations).[4] Chest CT may be more sensitive than chest radiograph (just like any non-COVID-19 pneumonia) and some chest CT findings may be characteristic of COVID-19.[1,4] Chest CT in patients with COVID-19 most commonly demonstrates ground-glass opacification with or without consolidative abnormalities having bilateral and peripheral distribution, and involve the lower lobes consistent with any viral (e.g. influenza) pneumonia.[1,3] COVID-19 pneumonia is again difficult to differentiate radiologically from community acquired pneumonia (CAP) especially if it is bilateral and caused by typical and atypical CAP organisms.

ARDS caused by severe COVID-19 exhibits similar radiological features like ARDS due to other aetiologies, however certain physiological features may be different in patients with COVID-19-associated ARDS.[2] Studies have floated the notion that in the early phase of COVID-19, severe hypoxaemia may be associated with high lung compliance and low alveolar recruitability (atypical ARDS), while in the later phase, severe hypoxaemia is

associated with low lung compliance and high recruitability (classic ARDS).[12] Refractory hypoxaemia in these patients can be managed with good response to prone positioning that may also be due to preserved lung compliance compared with patients who develop ARDS due to other causes.[1,4,12]

References

1. Irfan M, Mahmud T, Ashraf S, Langove MA, Zubairi AB, Afridi MZ, et al. Guidelines on Management of Patients with COVID-19. [Internet] Pakistan Chest Society. 2020 Mar [cited 2020 Apr 19]. Available from: http://www.pakistanchestsociety.pk/wp-content/uploads/2020/03/COVID-19-Management-guideline-PCS-28-March.pdf
2. Wu Z, McGoogan JM. Characteristics of and important lessons from the coronavirus disease 2019 (COVID-19) outbreak in China: summary of a report of 72314 cases from the Chinese Center for Disease Control and Prevention. JAMA 2020. doi: 10.1001/jama.2020.2648.
3. World Health Organization. Clinical management of severe acute respiratory infection when COVID-19 is suspected. Interim guidance. [Internet] 2020 Mar 13 [cited 2020 Apr 19] Available from URL: https://www.who.int/publications-detail/clinical-management-of-severe-acute-respiratory-infection-when-novel-coronavirus-(ncov)-infection-is-suspected
4. Wang D, Hu B, Hu C, Zhu F, Liu X, Zhang J, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus-infected pneumonia in Wuhan, China. JAMA 2020;323:1061-9. doi: 10.1001/jama.2020.1585.
5. World Health Organization. Home care for patients with COVID-19 presenting with mild symptoms and management of their contacts. Interim guidance. [Internet] 2020 Mar 17 [cited 2020 Apr 19]. Available from: https://www.who.int/publications-detail/home-care-for-patients-with-suspected-novel-coronavirus-(ncov)-infection-presenting-with-mild-symptoms-and-management-of-contacts
6. Cao B, Wang Y, Wen D, Liu W, Wang J, Fan G, et al. A trial of lopinavir-ritonavir in adults hospitalized with severe Covid-19. N Engl J Med 2020; NEJMoa2001282. doi: 10.1056/NEJMoa2001282.
7. Hinton DM. Request for Emergency Use Authorization For Use of Chloroquine Phosphate or Hydroxychloroquine Sulfate Supplied From the Strategic National Stockpile for Treatment of 2019 Coronavirus Disease. [Internet] Message to: Bright R. 2020 Mar 28 [cited 2020 Mar 30] [8 pages] Available from: https://www.fda.gov/media/136534/download
8. Shen C, Wang Z, Zhao F, Yang Y, Li J, Yuan J, et al. Treatment of 5 critically ill patients with covid-19 with convalescent plasma. JAMA 2020;323:1582-9. doi: 10.1001/jama.2020.4783.
9. Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. COVID-19: consider cytokine storm syndromes and immunosuppression. Lancet 2020;395:1033-4. doi: 10.1016/S0140-6736(20)30628-0.
10. McGrath JA, O'Sullivan A, Bennett G, O'Toole C, Joyce M, Byrne MA, et al. Investigation of the quantity of exhaled aerosols released into the environment during nebulisation. Pharmaceutics 2019;11:75. doi: 10.3390/pharmaceutics11020075.
11. Lansbury L, Rodrigo C, Leonardi-Bee J, Nguyen-Van-Tam J, Lim WS. Corticosteroids as adjunctive therapy in the treatment of influenza. Cochrane Database Syst Rev 2019;2:CD010406. doi: 10.1002/14651858.CD010406.pub3
12. Gattinoni L, Chiumello D, Caironi P, Busana M, Romitti F, Brazzi L, et al. COVID-19 pneumonia: different respiratory treatments for different phenotypes? Intensive Care Med 2020. 10.1007/s00134-020-06033-2.