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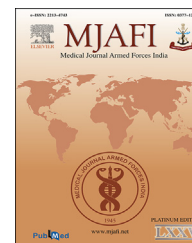
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Review Article

Management of COVID-19: A comprehensive and practical approach

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ABSTRACT

Since the beginning of Corona Virus Disease (COVID) pandemic, there has been lack of clarity about the management protocols in spite of frequently updated national and international guidelines. Irrational use of unproven therapies has not been helpful in improving treatment outcomes. Early use of high-dose steroids or late use of antiviral medicines might have caused more harm than the benefit. There is also lot of fear about post-COVID fibrosis leading to extended use of steroids and antifibrotics. We reviewed the available COVID guidelines and treatment protocols in the light of scientific evidence generated over last 2 years by a systematic literature search using various databases (PubMed, Google Scholar, MEDLINE, UpToDate, Embase, and Web of Science). This article presents a comprehensive approach to the diagnosis, appropriate investigations, their interpretations, and use of specific therapies according to the stage of disease.

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Introduction

In March 2020, World Health Organisation (WHO) declared Coronavirus Disease-19 (COVID-19) as a pandemic as it caused significant morbidity and mortality worldwide. The virus has been mutating frequently and various variants have emerged, the delta and omicron being the most prominent. The management of COVID-19 has evolved rapidly over the last 2 years, starting first with the use of repurposed drugs, oxygen therapy, ventilatory support, and other supportive therapies. Over a period of 2 years, better management protocols have emerged which have led to decrease in the morbidity and

mortality. This article describes evidence-based comprehensive approach to the management of COVID-19.

COVID-19 phases¹

COVID-19 progresses through various phases with certain degree of overlap and has distinct mechanisms involving each phase. These are as follows:

- *Viral replication phase* comprises of incubation period (2–14 days) and first week of symptomatic period. Antiviral medicines and monoclonal antibodies are used during this phase.

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- Inflammatory phase begins by end of replication phase. Steroids, immunomodulators, and anticoagulants are used during this phase.

Case definitions

These have been defined by Ministry of Health and Family Welfare (MOHFW)² for administrative and diagnostic purpose as summarized in Table 1.

Clinical stages³

Asymptomatic or pre-symptomatic stage: Persons testing positive by reverse transcription-polymerase chain reaction (RT-PCR) or Rapid Antigen Test (RAT) in the absence of symptoms.

Mild illness: Upper respiratory tract symptoms and/or fever without shortness of breath or hypoxia.

Moderate illness: Clinical/radiological signs of pneumonia, with respiratory rate (RR) ≥ 24 per minute and SpO₂ 90–93%.³ Oxygen saturation level must be carefully interpreted in patients with pre-existing respiratory illnesses like chronic obstructive pulmonary disease (COPD) or diffuse pulmonary lung diseases, who already have baseline hypoxia.³

Severe illness: Pneumonia with SpO₂ <90% or RR >30/min.³

Critical illness: Development of septic shock or ARDS.⁴

Evaluation and monitoring

Following features help in assessing severity and prognosis:

- Age more than 65 years and presence of co-morbidities predict poor outcome.⁴
- Duration of symptoms helps in determining specific therapeutic interventions.
- Persistent fever, dyspnea, and confusion indicate severity.⁵
- RR > 24/min is an indication for hospitalization.
- SpO₂ <94% on room air is an indication for hospitalization.³
- Chest radiography is sufficient for initial radiological evaluation.
- Computed tomography (CT) scan of thorax is not recommended for routine screening.^{6,7} It is useful only in following clinical scenarios:
 - a) Clinical features of COVID-19 but negative RT-PCR/RAT.⁸
 - b) Unexplained clinical deterioration where concurrent illness or thromboembolism needs exclusion.
 - c) Post-COVID-19 persistent hypoxia/impaired lung function (to differentiate post-COVID-19 lung fibrosis from other treatable causes).⁹

CT thorax findings¹⁰ are summarized in Table 2. These are, however, not specific to COVID-19 pneumonia.¹¹ CT severity score (CTSS) indicates the extent of lung involvement, but it should be carefully correlated with patient's hypoxia status as well as dyspnea severity, and the decision-making should not be

Table 1 – Case definitions.

Definition	Criteria
Suspect case	<p>A. A person who meets the clinical AND epidemiological criteria: Clinical criteria:</p> <ul style="list-style-type: none"> • Acute onset of fever AND cough; OR • Acute onset of ANY THREE OR MORE of the following signs or symptoms: Fever, cough, general weakness/fatigue, headache, myalgia, sore throat, coryza, dyspnoea, anorexia/nausea/vomiting, diarrhea, altered mental status. <p>AND epidemiological criteria:</p> <ul style="list-style-type: none"> • Residing or working in an area with high risk of transmission of virus: closed residential settings, humanitarian settings such as camp and camp-like settings for displaced persons; any time within the 14 days prior to symptom onset; or • Residing or travel to an area with community transmission any time within the 14 days prior to symptom onset; or • Working in any healthcare setting, including within health facilities or within the community; any time within the 14 days prior to symptom onset. <p>B. A patient with severe acute respiratory illness: (SARI: acute respiratory infection with history of fever or measured fever of $\geq 38^{\circ}\text{C}$; and cough; with onset within the last 10 days; and requires hospitalization).</p>
Probable case	<p>A. A patient who meets clinical criteria above AND is a contact of a probable or confirmed case, or linked to a COVID-19 cluster</p> <p>B. A suspect case with chest imaging showing findings suggestive of COVID-19 disease</p> <p>C. A person with recent onset of anosmia (loss of smell) or ageusia (loss of taste) in the absence of any other identified cause.</p> <p>D. Death, not otherwise explained, in an adult with respiratory distress preceding</p>
Confirmed case	<p>A. A person with a positive nucleic acid amplification test (NAAT) including RT-PCR or any other similar test approved by ICMR.</p> <p>B. A person with a positive SARS-CoV-2 RAT AND meeting either the probable case definition or suspect criteria OR</p> <p>C. An asymptomatic person with a positive SARS-CoV-2 RAT who is a contact of a probable or confirmed case.</p>

Table 2 – HRCT thorax findings in COVID-19.

Findings	%
Ground-glass opacifications (GGOs)	83
GGOs with mixed consolidation	58
Adjacent pleural thickening	52
Interlobular septal thickening	48
Air bronchograms	46

dictated by the CTSS alone. Follow-up CT scan is not recommended.¹²

- COVID-19 biomarkers (hematological and inflammatory) helps in risk stratification, monitoring and initiation of specific therapies:
 - 1) Hematological parameters: Lymphopenia and rising neutrophil-to-lymphocyte ratio predicts poor outcomes.^{13,14}
 - 2) Inflammatory markers
 - (a) C-reactive protein (CRP) and procalcitonin (PCT): Higher levels are associated with poorer outcome.¹⁵
 - (b) Interleukin 6 (IL-6): This correlates with extent of lung involvement.¹⁶
 - (c) Ferritin: Studies on ferritin levels have yielded unequivocal results.¹⁷
 - (d) D-dimer: This is a nonspecific marker of inflammation. Decrease in D-dimer along with CRP levels after treatment has good prognosis.¹⁸ However, Padua venous thromboembolism (VTE) score¹⁹ and D-dimer levels has poor correlation. D-dimer, therefore, should not be used as a sole marker for the presence of thrombosis.¹⁸ Studies from China²⁰ and India²¹ suggest that D-dimer level >2 µg/ml are good predictors of mortality.

Box 1**High-risk patients for monoclonal antibodies**

- Older age >65 years
- Obesity or being overweight (e.g. adults with BMI >25 kg/m², or, if age 12 to 17, have BMI ≥85th percentile for age and sex)
- Pregnancy
- Chronic kidney disease
- Diabetes mellitus
- Immunosuppression
- Cardiovascular disease (including congenital heart disease) or hypertension
- Chronic lung diseases (e.g., chronic obstructive pulmonary disease, asthma [moderate to severe], interstitial lung disease, cystic fibrosis, pulmonary hypertension)
- Sickle cell disease
- Neurodevelopmental disorders (e.g., cerebral palsy) or other medically complex conditions that confer medical complexity (e.g., genetic or metabolic syndromes and severe congenital anomalies)
- Dependence on a medical-related technology (e.g., tracheostomy, gastrostomy, or positive pressure ventilation [unrelated to COVID-19]).

- (e) Cardiac markers: Troponin and natriuretic peptides can be used in patients with known cardiac illness.²²
- (f) Lactate dehydrogenase (LDH): High levels are associated with increased mortality.¹³

Specific drug therapies

Choice of drugs depends on the phase of COVID-19.

Drugs used in viral replication phase**Monoclonal antibodies**

These antibodies target spike proteins and effectively decreases viral load, symptom duration, and mortality.^{23–25} Following categories of individuals are eligible for this treatment.

- (i) Patients with mild to moderate illness but not requiring oxygen OR
- (ii) Unvaccinated individuals with high risk of exposure to COVID-19 patients and any one of the risk factors as mentioned in [Text Box 1](#).^{26–29} Following three monoclonal antibodies are available:
 - **Casirivimab-imdevimab**: These human recombinant monoclonal antibodies bind to non-overlapping epitopes of spike protein.³⁰ The combined dose is 1200 mg IV/SC.³¹ The limiting factors for the usage of this drug in India is high cost and the problem of finding two eligible patients at the same time.
 - **Sotrovimab**: A single IV dose of 500 mg.³²
 - **Bamlanivimab-etesevimab**: These bind to overlapping epitopes of spike protein S1. It, however, has reduced susceptibility to both the gamma and beta variants.^{33,34} It is administered as a single IV dose of 700–1400 mg.

These antibodies should not be indiscriminately used for COVID-19 treatment as they work against delta but not against omicron variant (only sotrovimab appears to be effective in omicron).³⁵

Remdesivir

Remdesivir binds to viral RNA-dependent RNA polymerase and inhibits viral replication. It reduces recovery time in patients with moderate or severe disease.³⁶ In a meta-analysis,³⁷ remdesivir did not show mortality benefit compared with placebo. In an interim report of the SOLIDARITY trial³⁸ in hospitalized patients, remdesivir did not reduce 28-day mortality. ICMR guidelines² suggests use of remdesivir only in moderate or severe disease and strictly within 10 days of onset of symptoms. It is administered intravenously as 200 mg IV on day 1 followed by 100 mg daily for next 4 days. In a recent study, early administration of remdesivir in non-hospitalized patients showed some morbidity and mortality benefit.³⁹

Baricitinib

Baricitinib, a Janus kinase (JAK) inhibitor, has a potential antiviral effect through interference with viral entry into human cells. In a multinational, placebo-controlled, randomized trial,⁴⁰ for hospitalized adult cases, baricitinib with standard care reduced 28-day mortality. In another randomized trial⁴¹ of 1033 hospitalized adults, baricitinib plus remdesivir reduced time to recovery. Baricitinib is given in a dose of 4 mg orally once daily for up to 14 days. The dose is reduced in patients with renal insufficiency. Tofacitinib, another JAK inhibitor, may also have clinical benefit, although data are more limited.⁴²

Inhaled Budesonide

There has been under-representation of asthma and COPD patients admitted with COVID-19,⁴³ which was possibly due to extensive use of inhaled steroids in these patients. In vitro studies have shown that inhaled steroids reduce the replication of COVID-19 virus in airway epithelial cells⁴⁴ and also downregulates expression of ACE2 and TMPRSS2 genes,⁴⁵ which are essential for viral entry. Steroids in COVID-19 trial (STOIC)⁴⁶ and the PRINCIPLE trial⁴⁷ showed that early administration of inhaled budesonide reduced requirement of urgent medical care and recovery time but had no effect on risk of hospitalization or mortality. This therapy has also now been recommended by ICMR.²

Favipiravir

Favipiravir inhibits viral RNA polymerase enzyme, thereby preventing replication and transcription of the viral genome.⁴⁸ Clinical trials have not shown uniform results as regards the efficacy of favipiravir.^{49–51} This drug also has been used extensively in our country, and its usage may be justified in view of paucity of other effective therapies (except for monoclonal antibody cocktail therapy, which is steeply priced) and its fairly good safety profile. Dosage schedule is 1800 mg twice a day on day 1 followed by 800 mg twice daily for 7 days. However, in view of nonuniformity of results of clinical trials data, none of the international guidelines (IDSA

guidelines, WHO guidelines, NIH guidelines) recommend use of favipiravir.⁴⁹

Molnupiravir

This is an oral, antiviral nucleoside analogue which inhibits SARS-CoV-2 replication and is active against prevalent viral variants. In a clinical trial, among over 750 nonhospitalized adults who had onset of mild to moderate COVID-19 within 5 days and at least one risk factor for severe disease, molnupiravir reduced the risk of hospitalization or death by approximately 50%, all eight deaths in the trial occurred among placebo recipients.⁵² The dose is 800 mg twice daily for 5 days. It has got a potential teratogenic action; hence, it is contraindicated during pregnancy and contraception should be followed for at least 3 months following its use, even by the male partner.

PF-07321332/Ritonavir

This is a combination of oral protease inhibitors, PF-07321332 plus ritonavir. PF-07321332 blocks the activity of the CoV-2-3CL protease, an enzyme required for viral replication. Addition of ritonavir slows the metabolism of PF-07321332, so as to increase its bioavailability. In a trial including 1219 adult outpatients with at least one risk factor for severe disease, PF-07321332/ritonavir, administered within 3 days of symptom onset, reduced the risk of hospitalization or death at 28 days by 89 percent compared with placebo.⁵³

Other drugs with potential anti-viral activity

Many other repurposed drugs with known antimicrobial effects have been proposed for use in COVID-19 patients but have insufficient evidence of clinical benefit and have not been recommended by international and national guidelines. These are ivermectin, hydroxychloroquine/chloroquine, interferon beta, lopinavir + ritonavir, and convalescent plasma.

Drugs used in inflammatory phase

Dexamethasone and other glucocorticoids

In a large, randomized, open-label trial, dexamethasone has been shown to decrease mortality at 28 days in patients with moderate to severe disease.^{54,55} In a meta-analysis of seven trials,³⁶ glucocorticoids reduced mortality at 28 days. The dosage schedule used in recovery trial was dexamethasone 6 mg once a day for 10 days.^{54,55} However, methylprednisolone in equivalent dosages (8 mg every 6 h or 16 mg every 12 h) may also be used.⁵⁶

IL-6 pathway inhibitors

Increased level of cytokines (IL-6) along with other inflammatory markers are associated with poor outcome. Blocking the inflammatory pathway may prevent disease progression.⁵⁷ Three drugs approved for use in COVID-19 illness includes tocilizumab, sarilumab, and siltuximab.

RECOVERY trial⁵⁸ and REMAP-CAP trial⁵⁹ revealed that tocilizumab reduces mortality at 28 days. Cochrane database systemic review⁶⁰ and a meta-analysis⁶¹ also showed mortality benefit of these drugs. The indications of use of tocilizumab and sarilumab are as follows:

- Recently hospitalized patients (i.e., within first 3 days) with severe illness requiring intensive care.
- Recently hospitalized patients (i.e., within first 3 days) not requiring intensive care but with worsening hypoxia and raised inflammatory markers, for example, CRP.

Tocilizumab is given in dose of 8 mg/kg body weight (maximum up to 800 mg) along with dexamethasone. A second dose may be considered if there is either no improvement or deterioration. There has been increase in usage of measurement of IL-6 value before administration of these drugs. It may not be necessary, since CRP is cost-effective and correlates well with serum IL-6 concentrations. CRP >50 mg/L suggests severe disease and concentration of around 75 mg/L distinguishes fatal from nonfatal cases.⁵⁸ Contraindications for tocilizumab are: severe immunosuppression, liver enzymes >5 times of normal, uncontrolled serious infections, and platelet count <50,000 cells/ μ L.³² Use of tocilizumab in pregnancy is not recommended due to insufficient data.³² Data regarding efficacy of siltuximab in COVID-19 is limited.⁶²

Other immunomodulatory drugs

Immunomodulatory agents like IL-1 inhibitors,⁶³ other cytokine inhibitors,⁶⁴ kinase inhibitors,⁶⁵ complement inhibitors,⁶⁶ bradykinin pathway inhibitors,⁶⁷ and hematopoietic colony-stimulating factors agonist and antagonists⁶⁸ are being evaluated.

Anticoagulants

COVID-19 leads to various coagulation abnormalities which may give rise to VTE and pulmonary embolism (PE).⁶⁹ A study revealed significant increase in most of the coagulation parameters among COVID-19 nonsurvivors compared with survivors.⁷⁰ All COVID-19 patients with acute and critical illness should receive prophylactic dose of anticoagulation medicines as recommended by various guidelines.^{70–72} Therapeutic dose of anticoagulants is indicated in patients with high probability of thromboembolic events and when diagnostic imaging is not possible.³² Anticoagulants should also be considered if D-dimer levels are disproportionately higher than other inflammatory markers, and patient has other VTE risk factors.²⁰ Post-discharge VTE prophylaxis should be reserved for patients with risk factors for VTE.³² It needs to be reemphasized that D-dimer must be considered along with risk factors for management of thromboembolic events.

Other drug therapies

- Azithromycin

This drug was over prescribed during first and second waves of COVID-19 for its presumptive anti-viral and immunomodulatory effects. However, clinical trials have failed to demonstrate any clinical benefit.^{73,74}

- Vitamin C and zinc

Clinical trials done in COVID-19 patients, did not reveal any therapeutic benefit when received 10 days of vitamin C, zinc, or both.^{75,76}

- Vitamin D

Studies involving administration of vitamin D in hospitalized COVID-19 patients revealed no significant differences in length of hospital stay and in-hospital mortality.^{77–79}

- Antibiotics

Empirical antibiotics therapy may be indicated in COVID-19 patients if there is clinical suspicion (unexplained clinical deterioration, new radiological opacities) of superadded bacterial infections. Procalcitonin levels should not be used as a marker for determining severity of bacterial infection in COVID-19 patients, since procalcitonin levels has also been found to be raised in COVID-19 infection.⁸⁰

Symptomatic treatment

For fever, tablet paracetamol 500 mg three to four times a day and in case fever is not resolving other nonsteroidal anti-inflammatory drugs (such as tablet Naproxen 250 mg twice a day) can be given.²

Oxygen therapy

Oxygen therapy has been the cornerstone in the management of hospitalized COVID-19 patients. Its role got much more significance since there was no definitive therapies especially during the early phase of COVID-19. Salient features that will help in delivering oxygen therapy in a most effective manner includes the following:

- Supplemental oxygen therapy should be given in COVID-19 patients when SpO₂ is <92%.⁸¹
- The target SpO₂ with supplemental oxygen should be between 92% and 96%.³²
- Oxygen therapy should be delivered through appropriate device depending on the severity of hypoxia and work of breathing.

High-flow nasal cannula and noninvasive ventilation

Patient should be switched over to either high-flow nasal cannula (HFNC) or noninvasive ventilation (NIV) if oxygen requirement is > 10L/min and there is increase work of breathing. HFNC is usually preferred in view of comfort and convenience to the patient. Recommended settings of HFNC and NIV in patients with severe Covid-19 are as follows.^{82–86}

- Suggested NIV settings: Pressure support of 5–15 cm H₂O, target tidal volume of 5–7 ml/kg, and PEEP of 5–10 cm H₂O and FiO₂ as required to maintain SpO₂ >94%.
- Suggested HFNC settings: Initial flow rate should be 20–30L/min with maximum of 60L/min.
- As HFNC and NIV are considered aerosol generating procedures, infection prevention control measures should be strictly followed.

Table 3 – Summary of treatment.

Stages	Mild illness	Moderate illness	Severe illness	Critical illness
Criteria	Fever, cough, malaise no dyspnea (SpO ₂ > 94% room air)	E/o LRTI with SpO ₂ ≥ 94% room air and RR ≥ 24/min.	Signs of pneumonia with SpO ₂ < 90% room air and /RR > 30/min.	Development of ARDS/SEPSIS/ SEPTIC SHOCK*
Place of management	Home isolation Self-monitoring	Hospitalization in ward	ICU care	ICU care
Investigations	None	CBC, LFTs, RFTs, BSL, ECG, chest X-ray CRP, LDH, D-dimer (repeat every 72 h) HRCT chest as per indications	CBC, LFTs, RFTs, BSL, ECG, chest X-ray CRP, LDH, D-dimer (Repeat every 72 h) HRCT chest, 2D ECHO, PCT, troponin, if indicated	CBC, LFTs, RFTs, BSL, ECG, chest X-ray CRP, LDH, D-dimer (repeat every 72 h) HRCT chest, 2D ECHO, PCT, troponin, if indicated
Specific drug therapy	IV/SC 600 mg casirivimab and 600 mg imdevimab as per indications Inhaled budesonide 400 ug 2 puffs BD Tab molnupiravir 800 mg BD for 5 days	Oxygen therapy if SpO ₂ < 92% Target SpO ₂ : 92–96% Inj. remdesivir 200 mg IV on day 1 followed by 100 mg IV daily for 4 days Inj. Dexamethasone 6 mg IV OD or Inj. methylprednisolone 16 mg IV BD for 10 days ⁵⁶ LMWH prophylactic dose Enoxaparin: 40 mg OD Antibiotics: Amoxi-clav, cefuroxime if indicated	Oxygen therapy HFNC/NIV Target SpO ₂ : 90–94% Inj. remdesivir if duration of disease less than 10 days Inj. tocilizumab if CRP > 75 mg/L Inj Dexamethasone 6 mg IV OD/Inj methylprednisolone 16 mg IV BD for 10 days ⁵⁶ LMWH prophylactic Enoxaparin: 40 mg OD	Ventilatory management of ARDS Inj. tocilizumab if CRP > 75 mg/L Taper off steroids Enoxaparin: 40 mg BD if thromboembolic events suspected Antibiotics: Amoxi-clav, cefuroxime if indicated
Monitoring	Monitor difficulty in breathing, temperature and oxygen saturation Contact physician in case of difficulty in breathing, persistent fever, persistent cough more than 5 days and SpO ₂ < 93%	Monitor breathing rate, hemodynamic instability, change in oxygen requirement	Monitor for signs of disease progression (RR > 30, FiO ₂ requirement > 60% to maintain SpO ₂ of 90%, increased work of breathing, altered sensorium and hemodynamic instability)	Monitor for signs of disease progression (RR > 30, FiO ₂ requirement > 60% to maintain SpO ₂ of 90%, increased work of breathing, altered sensorium and hemodynamic instability) Close monitoring of ventilatory parameters like Peak inspiratory pressure (PIP), plateau pressure and PEEP

Table 4 – Post-COVID-19 conditions.

1	Cardiovascular	Dilated cardiomyopathy, heart failure, pericarditis
2	Pulmonary	Pulmonary fibrosis, reactive airway dysfunction
3	Renal	Chronic kidney disease
4	Dermatologic	Alopecia
5	Rheumatologic	Reactive arthritis, fibromyalgia, CTDs
6	Endocrine	Diabetes mellitus, hypothyroidism
7	Neurologic	Transient ischemic attack/stroke, sleep dysregulation, altered cognition, memory impairment, headache, fatigue, and neuropathy
8	Psychiatric	Depression, anxiety, and post-traumatic stress disorder, psychosis
9	Hematologic	Pulmonary embolism, arterial thrombosis, venous thromboembolism
10	Urologic	Incontinence, sexual dysfunction
11	Others	Relapsing fevers, weight loss, dysautonomia, vitamin D deficiency, and progression of comorbid conditions

Table 5 – Vaccines against COVID-19.

Sr. No	Vaccine name	Manufacturer	Type of vaccine	Dose	Efficacy
Vaccines in use					
1	Covaxin	Bharat Biotech	Inactivated	2	81.6%
2	Covishield	Oxford-AstraZeneca	Viral vector	2	81.3%
3	Sputnik V	Gamaleya	Viral vector	2	91.6%
4	Corbevax	Biological E	Protein sub-unit	2	80%
Approved vaccines					
1	mRNA-1273	Moderna	mRNA	2	94.5%
2	Ad26.COVS. S	Johnson and Johnson	Viral vector	2	66.3%
3	ZyCoV-D	Cadila Healthcare	DNA	3	67%
4	Covovax	Serum Institute of India	Protein sub-unit	2	90%

- Patients on HFNC and NIV should be closely monitored and in case of rapid disease progression (RR > 30, FiO₂ requirement >60% or flow rate of >60 L/min in HFNC to maintain SpO₂ of 90%, increased work of breathing, altered sensorium, hemodynamic instability, and multi-organ failure etc.) must be quickly switched over to invasive ventilation.

Invasive mechanical ventilation

Since intubated patients usually have moderate to severe ARDS, ventilation should be delivered by using *lung protective ventilation strategy using ARDS net protocol*.^{87–89} The settings should be: tidal volume of 6 ml/kg, RR of 15–35/min, PEEP of 5–15 cm H₂O, target plateau pressure of <30cm H₂O, target SpO₂ 88–95% and/or PaO₂ 55–80 mm of Hg.

Prone ventilation:

- Early self-proning is recommended in awake, non-intubated patients. Care must be taken not to disrupt oxygen flow during rotation of the patient.⁹⁰
- Prone ventilation is typically given for 30–120 min; initially in prone position followed by left lateral decubitus, right lateral decubitus and upright sitting position.
- In ventilated patients, prone ventilation for 12–16 h has been shown to reduce mortality in various meta-analysis.⁹¹

It also leads to increase in the risk of pressure sores and endotracheal tube obstruction.⁹²

The treatment protocol described above has been summarized in [Table 3](#).

Post-COVID-19 conditions

- Post-COVID-19 or long COVID-19 is the term used for the health consequences that are present 4 or more weeks after COVID-19 infection.⁹³ These can be due to multi-organ complications, treatment given, hospitalization, or because of COVID-19 itself.^{94,95}
- Post-COVID-19 conditions^{96–100} are summarized in [Table 4](#).
- The management of post-COVID-19 conditions should be focused on optimizing function and quality of life.^{101,102} Treating physician along with other concerned specialists must develop comprehensive management plan customized to individual patients.¹⁰³ Since post-COVID-19 pulmonary fibrosis is quite common and more serious condition, it needs little more elaboration.

Post-COVID-19 pulmonary fibrosis

- Pathogenesis of post-Covid-19 pulmonary fibrosis includes excessive collagen deposition and failed alveolar re-epithelization disrupting the normal lung architecture.

- There is no consensus about the type of “fibrotic-like” sequelae in post-COVID-19 patients.¹⁰⁴ It has been described as either organizing pneumonia,¹⁰⁵ interstitial lung disease,¹⁰⁶ pulmonary fibrosis,¹⁰⁷ or fibrotic lung disease.^{108,109}
- Fibrosis was clinically confirmed in 56% and 71% of the patients with moderate and severe illness respectively.¹¹⁰ Risk factors for pulmonary fibrosis includes old age, severe ARDS, mechanical ventilation, history of smoking, and chronic alcoholism.
- The diagnosis is made by clinical symptoms and characteristic CT findings.

Based on the presumptions that pathogenesis of post-COVID-19 pulmonary fibrosis and idiopathic pulmonary fibrosis have some similarities, anti-fibrotic drugs (pirfenidone and nintedanib) have been increasingly used in such patients. However, there is no definitive evidence for or against the use of these drugs. We will have to wait for conclusive evidence from the ongoing clinical trials for these two, and some other newer drugs for post-COVID-19 pulmonary fibrosis. Till then, pulmonary rehabilitation program and long-term oxygen treatment should be included as a part of comprehensive treatment for pulmonary fibrosis due to COVID-19.

Prevention of COVID-19

COVID-19 appropriate behaviors plays an important role in prevention of COVID-19. In addition, the availability of various vaccines has also contributed significantly in prevention of disease. Four vaccines, that is, Covishield, Covaxin, Sputnik-V, and Corbevax are in use at present. Characteristics of these four and other approved vaccines are mentioned in Table 5. Vaccine induced immunity mostly targets spike protein of COVID-19 virus. Omicron variant has the ability to reduce neutralizing activity of vaccine, hence appears to be less effective against currently available vaccines.¹¹¹ The potential impact of the COVID-19 vaccines is still being analyzed against this new variant.

Disclosure of competing interest

The authors have none to declare.

Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.mjafi.2022.06.020>.

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