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Clinical management of COVID-19

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The novel coronavirus disease 2019 (COVID-19) with its early origin from Wuhan city in China has evolved into a global pandemic. Maximal precautionary measures and resources have been put forward by most nations in war footing to mitigate transmission and decrease fatality rates. This article was aimed to review the evidence on clinical management and to deal with the identification of high-risk groups, warning signs, appropriate investigations, proper sample collection for confirmation, general and specific treatment measures, strategies as well as infection control in the healthcare settings. Advanced age, cardiovascular disease, diabetes, hypertension and cancer have been found to be the risk factors for severe disease. Fever lasting for >five days with tachypnoea, tachycardia or hypotension are indications for urgent attention and hospitalization in a patient with suspected COVID-19. At present, reverse transcription-polymerase chain reaction (RT-PCR) from the upper respiratory tract samples is the diagnostic test of choice. While many drugs have shown *in vitro* activity against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), there are insufficient clinical data to promote or dissuade their usage. Among the currently available drugs, hydroxychloroquine and lopinavir/ritonavir may be considered for patients with severe COVID-19 infection, awaiting further clinical trials. Stringent droplet and contact precautions will protect healthcare workers against most clinical exposures to COVID-19.

Key words Clinical management - corticosteroids - COVID-19 - hydroxychloroquine - lopinavir - remdesivir - risk groups - SARS-CoV-2

Today, the world stands in the combat against the coronavirus disease 2019 (COVID-19), an unfolding viral pandemic exacting a significant toll on the human race. With its beginnings in Wuhan city, China, as a cluster of cases of pneumonia with unidentified aetiology, it was soon identified to be caused by a novel strain of coronavirus (CoV), now named severe acute respiratory syndrome CoV-2 (SARS-CoV-2), which spread primarily through droplets, respiratory secretions and direct contact[1,2]. As of mid-April 2020, the infection has spread to over 185 countries, infected more than two million people and resulted in over 127,000 deaths globally[3].

COVID-19 in majority of the population (80%) presents as an asymptomatic or mild infection[4]. However, the disease is known to cause severe pneumonia and multiple complications, especially in certain high-risk groups. These remaining 20 per cent of infected patients will need admission and hospital care, including five per cent of them who require intensive care and ventilator support[4]. Multiple protocols and management strategies are currently

being developed worldwide to overcome this issue. However, in resource-limited settings like India which deal with a huge population base, it is critical for the doctors to be well equipped to speedily identify and treat patients who require admission and critical care. This will ensure proficient utilization of resources and facilities available without overburdening the existing healthcare system. Thus, an attempt was made to summarize the clinical management of COVID-19 for Indian physicians.

High-risk groups

COVID-19 is peculiar in its disproportionate case fatality rates among patients >60 yr as opposed to young adults or paediatric population. The highest mortality rates were seen among individuals above 80 yr of age at 14.8 per cent. These results were brought out in one of the largest data analyses conducted in China involving 72,314 patient records[5]. While patients with no prior comorbid conditions had a case fatality rate of 0.9 per cent, it was notably higher among those with specific underlying comorbidities, making these population groups high-risk and more vulnerable to severe COVID-19[5]. These high-risk groups and age-wise case fatality rates are depicted in Table I. While further research is going on, the data suggests that tobacco smoking is also a risk factor for COVID-19. Smokers (both former and current) are more likely to have severe symptoms, are admitted to intensive care unit (ICU), need mechanical ventilation or die compared to non-smokers[6,7].

It is imperative to recognize these susceptible groups, educate them regarding the infection and precautionary measures as well as be aware of their tendency for worse outcomes (Table I). When treating such patients, a multidisciplinary approach is preferred with a keen eye to avoid unwarranted polypharmacy and adverse drug reactions[8].

Table I. Comorbid illness and case fatality rates in high-risk groups

Age, yr (case fatality rate, %)	Comorbid illness (case fatality rate, %)
60-70 (4)	Cardiovascular disease (10.5)
>70-80 (8)	Diabetes mellitus (7.3)
>80 (15)	Chronic respiratory disease (6.3)
	Systemic hypertension (6.0)
	Cancer (5.6)

Source: Ref. 5

Symptoms and warning signs

The incubation period of COVID-19 is 1-14 days (mean duration of 5-7 days), with peak viraemia occurring before the onset of symptoms. This underlines the transmission potential of asymptomatic or minimally symptomatic patients[2,9,10]. The most common presenting features of COVID-19 infection are fever (80-90%), cough (60-80%) and dyspnoea (18-46%). Other symptoms at presentation include myalgia or fatigue, sore throat, nasal congestion, headache, nausea, vomiting and diarrhoea[6,11]. On examination, findings of pneumonia may be present in a minority[8]. Warning signs or red flag signs that can assist in triage, indicating the need for urgent care, are summarized in Table II.

Laboratory findings

Alteration in laboratory parameters may provide insight into the pre-test probability of an underlying COVID-19 infection. While total counts are normal in majority of the patients, leucopenia may be seen in one-third but leucocytosis is rare (<10%)[6]. Lymphocytopenia is commonly recognized in these patients[6]. The common laboratory abnormalities seen with COVID-19 infection are summarized in Table III. Procalcitonin levels are typically not elevated, and the presence of elevated levels should raise the suspicion of a superadded bacterial infection[12]. Chest X-rays/imaging are often abnormal even in early disease and reveal bilateral, peripheral and ill-defined interstitial infiltrates with ground-glass opacification or lobular and subsegmental consolidation[11,13,14].

Table II. Symptoms and warning signs

Symptoms (frequency in %)	Warning signs (needs hospitalization)
Fever (80-90) Cough (60-80) Breathlessness (18-46) Fatigue (38) Body ache/joint pain (15) Sore throat (11-14) Headache (6-14) Chills (12) Body ache/joint pain (15) Running nose (5) Nausea/vomiting (5) Diarrhoea (2-10)	Fever and upper respiratory symptoms lasting for >5 days and any of the following: Breathlessness/respiratory rate >24/min Oxygen saturation (SpO_2) <95% in room air Fatigue with heart rate of >110/bpm Systolic blood pressure <90 mmHg

bpm, beats per minute
Source: Refs 6, 11

Complications

COVID-19 can take a rapidly progressive and fulminant course, giving rise to various complications that could result in a fatal illness. The common complications seen with COVID-19 are summarized in Table III[6,11,14]. Some of the rare complications that have been reported include rhabdomyolysis and disseminated intravascular coagulation[6]. Early suspicion and intensive monitoring for these complications as well as prompt, appropriate supportive measures may help reduce untoward outcomes.

Categorization of disease severity, testing and admission strategy

During the pandemic period, when a patient presents to the emergency department with fever, cough or breathlessness, a high level of suspicion for COVID-19 infection must be entertained. The physician must keep a watch for the warning signs and initiate early resuscitative and supportive measures if these are detected. Table IV elaborates the categorization of suspected COVID-19 patients into mild, moderate and severe disease based on their presenting symptoms and signs. Most patients with COVID-19 have self-resolving mild disease mimicking other upper respiratory infections. Hence, they are low priority for testing and can be safely managed with home isolation[16]. The suggested testing strategy and the level of care based on the disease severity and risk category are summarized in Table IV.

Careful triaging of patients with COVID-19, at the time of first contact with the healthcare system, will help prioritize patients based on the risk group, critical nature and severity of illness as well as resources available. These measures will help decrease the load on the hospitals by reducing unnecessary admissions to the inpatient wards and ICUs, allowing for the allocation of hospital beds, ventilators and supportive devices to patients with more severe disease. In addition, this might prevent burnout among treating healthcare workers and reduce transmission in the hospital.

Sample collection and laboratory confirmation

Sample collection for the detection of SARS-CoV-2 infection should be carried out as early as possible in patients with suspected COVID-19 falling into the moderate and severe groups. The high upper respiratory viral load in COVID-19 makes nasopharyngeal swab the recommended sample for confirmatory testing. Sputum collection and testing should be considered only for patients with productive cough, while the

Table III. Laboratory abnormalities and complications

Laboratory abnormalities	Complications
CBC: Lymphopenia	Pneumonia
Creatinine↑	ARDS
AST/ALT/bilirubin ↑	Hypotension
CRP ↑, LDH ↑, ferritin ↑	Myocarditis
CXR: Interstitial infiltrates/ARDS	Acute kidney injury

AST, aspartate aminotransferase; ALT, alanine aminotransferase; LDH, lactate dehydrogenase; CRP, C-reactive protein; ARDS, acute respiratory distress syndrome; CXR, chest X-rays; CBC, complete blood count
Source: Refs 6, 11, 14

Table IV. Categorization of probable coronavirus disease 2019 (COVID-19) severity, testing and admission strategy

Clinical category of COVID-19	Features	Testing strategy	Level of care
Mild	Fever with upper respiratory symptoms Mild sore throat and GI symptoms Testing may be considered in select individuals in the high-risk group	Low priority	Home care
Moderate	Breathlessness/respiratory rate >24/min Oxygen saturation (SpO_2) <95% in room air Fatigue with heart rate of >110/bpm Systolic blood pressure <90 mmHg	High priority	Inpatient care
Severe	SpO_2 <90% in room air Hypotension requiring ionotropic support ARDS/myocarditis	High priority	Intensive care

GI, gastrointestinal
Source: Ref. 15

induction of sputum is not advised as aerosols produced by the procedure can facilitate disease transmission. For intubated patients, a lower respiratory tract aspirate or bronchoalveolar lavage sample is preferred. Swabs are to be placed in a viral transport medium and transported on ice to the laboratory. Hospital staff responsible for collecting, transporting, testing and analysis of the respiratory samples must ensure the usage of appropriate personal protective measures.

The recommended diagnostic test is the reverse transcription-polymerase chain reaction (RT-PCR) on respiratory samples. Though initial studies revealed low sensitivities of 30-60 per cent, newer assays show improved results[17]. Based on the CoV grouping criterion, *RdRp* (RNA-dependent RNA polymerase) gene assay with a lower level of detection of 3.8 copies per reaction at 95 per cent detection probability is considered the reference standard PCR[18].

The U.S. Food & Drug Administration (FDA) has recently approved a rapid diagnostic test capable of providing the results within 45 minutes[19]. Cepheid's COVID-19 test, a molecular PCR-based assay, has succeeded in demonstrating high accuracy using the company's GeneXpert machine[19]. Antibody detection may reveal positivity about a week after the onset of illness and hence has no role in the diagnosis in the first week of illness. However, it will be a cost-effective test for diagnosis in the second week of illness. In addition, it is expected to be useful in epidemiological studies in the estimation of community prevalence of the disease. Antigen tests, while still in the conceptual and design stage, once developed will provide rapid results and may be carried out as the point-of-care test.

General treatment measures

Patients are categorized based on the severity of disease (Table IV) for further decisions on hospitalization and treatment options. The treatment includes antiviral drugs or specific therapy and supportive management of complications, including advanced organ support, if required. The theoretical concern that non-steroidal anti-inflammatory drugs (NSAIDs) worsen outcomes in COVID-19 infections as these upregulate angiotensin-converting enzyme 2 (ACE-2) levels in the lung, the entry receptor for the virus, remains yet to be proven[20]. Small studies have also revealed that NSAID exposure is independently associated with the occurrence of pleuro-pulmonary complications in patients with community-acquired pneumonias[21]. For the above reasons, paracetamol may be preferred over NSAIDs in COVID-19 management.

The mechanism of lung injury produced by COVID-19 also appears to be through its effect on ACE-2, though this has not yet been confirmed. This has in turn led to the hypothesis that patients with cardiac diseases, hypertension or diabetes being treated with ACE inhibitors or angiotensin receptor blockers are at higher risk for severe COVID-19 infection as they upregulate increased ACE-2 receptor expression[20]. There is no clear clinical evidence for the same and hence, cessation or a change in medication for the general population on regular treatment with ACE inhibitors or angiotensin II receptor blockers (ARBs) for the underlying comorbid disease is not recommended[22]. However, change to an alternate regimen may be considered for patients who are admitted and positive for COVID-19 for the period of their illness. These decisions need to be made by the treating team on a case-by-case basis after taking into consideration the patient's underlying comorbidity and weighing the potential risks and benefits.

Specific treatments and treatment strategy

With the evolving challenges brought about by this public health emergency, there is a pressing need for the timely identification and development of drugs that can be used in the treatment of COVID-19 infections. A wide range of drugs that have earlier been approved for other indications as well as several investigational drugs are being studied through clinical trials for benefit in COVID-19[23]. As the COVID-19 pandemic evolves, more and more scientific data supporting various management and treatment options have been brought to light. However, it is of utmost importance for the treating physician to exercise caution and critically appraise the available data prior to incorporating various pharmaceutical agents into clinical practice.

At present, the role of specific antiviral medication is at best adjunctive in nature. The following drugs have shown some promise for the management of COVID-19:

Hydroxychloroquine and chloroquine

One of the earliest trials conducted in China in an attempt to discover the role of the existing drugs against COVID-19 infection revealed that chloroquine has *in vitro* activity against SARS-CoV-2[24]. Subsequent *in vivo* trials confirmed

that treating novel CoV pneumonia with chloroquine might improve the success rate of treatment, shorten hospital stay and improve patient outcomes[25,26]. The 4-aminoquinolone, commonly used as an antimalarial and anti-inflammatory agent, possesses broad antiviral activity. While the exact mechanisms are unknown, it is considered to gain its antiviral effects through alkalinization of the phagolysosome as well as inhibition of viral entry by blocking receptor binding and membrane fusion[25,27]. With a similar mechanism of action, hydroxychloroquine (HCQ) has demonstrated more potent *in vitro* inhibition of SARS-CoV-2 virus compared to chloroquine[28]. Its fewer side effects, safety in pregnancy and inexpensive nature makes it more preferable to chloroquine[27-30]. In a small cohort of heterogeneous French patients, HCQ has been shown to reduce SARS-CoV-2 viral loads at day 6 compared to controls[31]. However, this study has been criticized widely for its methodological flaws. If chosen for the treatment of confirmed COVID-19, the dose of HCQ suggested is 400 mg twice a day (bd) for one day followed by 200 mg (bd) for 5-10 days. Another small randomized controlled trial failed to show any significant benefit[32]. While HCQ has been suggested as an option for prophylaxis for healthcare workers who are taking care of COVID-19 patients and household contacts of laboratory-confirmed patients, the potential benefit must be weighed against the increased risk of life-threatening arrhythmias[33]. The QT interval must be monitored with frequent electrocardiographs (ECGs).

Lopinavir/ritonavir

Lopinavir/ritonavir, a boosted protease inhibitor combination, while commonly used in the treatment of HIV-1 infection, came into spotlight during the SARS outbreak in 2003 when it was proved to have *in vitro* activity against the causative SARS-CoV[34]. Lopinavir is probably the only agent studied in a randomized controlled trial (RCT). While the agent was not shown to be beneficial with regard to the primary end point (time to clinical improvement), the lopinavir arm had numerically lesser deaths and ventilator days. However, the drug did not reduce the viral loads when compared to the control arm. The dose used was lopinavir 400 mg-ritonavir 100 mg twice a day for 14 days[35].

Oseltamivir

Oseltamivir, a neuroaminidase inhibitor, is a pivotal drug in influenza management. It has not been shown to have activity for CoVs due to lack of neuraminidase and is hence unlikely to be of benefit. Though it was used in the earlier part of the epidemic in China, it is no longer recommended by most guidelines[8,36].

Remdesivir

Remdesivir, an adenosine analogue and RNA polymerase blocker, is a novel drug developed for the treatment of Ebola virus infection. A randomized control trial on remdesivir in severe COVID-19 patients did not show any significant benefit. However, there was a trend towards shortened illness in patients who received the drug early[37]. While the drug is available in different countries through multiple clinical trials, it is also being provided by the manufacturers on a compassionate use basis. In view of its broad antiviral properties, safety profile from Ebola studies and *in vitro* activity against SARS-CoV-2, remdesivir is considered as a promising agent[23,24,38]. A recent case series of the drug in a compassionate use programme in COVID-19 patients with hypoxemia showed clinical improvement in two-thirds of the patients[39].

Favipiravir

Favipiravir, a RNA polymerase inhibitor, has shown modest activity against SARS-CoV-2 virus with pronounced cytopathy in Vero cell studies[24] The drug has been used in China for the treatment of COVID-19 and is being studied in a clinical trial for mild SARS-CoV-2 disease and also as an adjunct agent in moderate and severe diseases[40].

Interleukin-6 (IL-6) inhibitors

A subgroup of patients with COVID-19 develop severe cytokine activation and secondary haemophagocytic lymphohistiocytosis (HLH), leading to rapid-onset hypoxemia, shock and multiorgan dysfunction[41]. A higher neutrophil count and elevated C-reactive protein may predict this subgroup of patients[42,43]. Interleukin-6 (IL-6) is a key cytokine in the cytokine storm, and tocilizumb, a humanized anti-IL-6 receptor antibody, is proposed as a therapeutic agent in severe SARS-CoV-2 disease. Anecdotal reports from Italy and China support the use of tocilizumab in this setting[44]. In a small series of 21 patients with severe or critical COVID-19 from China, tocilizumab showed marked improvement in hypoxia, chest imaging, fever, lymphocyte counts and C-reactive protein. Most of the patients included in this series had IL-6 levels elevated more than 20-fold[45].

Corticosteroids

Corticosteroids are generally not useful against similar severe respiratory viral illnesses such as SARS or Middle East respiratory syndrome (MERS)-CoV disease. A recent retrospective review showed decreased likelihood of death among patients with SARS-CoV-2-related acute respiratory distress syndrome (ARDS) who received methylprednisolone (hazard ratio: 0.38; 95% confidence interval: 0.20-0.72)[42]. Steroids can be used if indicated for another reason such as accompanying severe asthma and septic shock. However, the clinical team should weigh the potential small benefits against risks such as poor suppression of viral loads and prolonged shedding as noted in other illnesses such as MERS-CoV disease[46,47].

Convalescent plasma from COVID-19 survivors

Uncontrolled studies during the SARS epidemic showed that convalescent plasma therapy decreased hospital stay and mortality when used in the critically ill[48]. Convalescent plasma therapy was attempted with some benefit in MERS, Ebola and H1N1 pandemic influenza[49-51]. A small case series of five patients with critically ill COVID-19 on mechanical ventilation improving after receiving therapy on the third week of illness is encouraging[52]. Depicted in Table V is a quick guide for adjunctive treatment strategy to be considered on the use of specific antivirals for the management of COVID-19 patients depending on the clinical category and severity of illness.

Management of critically ill COVID-19 patient

Severe SARS-CoV-2 pneumonia may require supportive intensive care. Lung protective ventilation strategies, careful fluid monitoring, prone ventilation and when clinically indicated extracorporeal membranous oxygenation have been recommended in the management of the critically ill. However, certain aspects of intensive care are unique in view of the pathology and risk to healthcare workers, and these unique features are summarized below:

Pulmonary management in critically ill COVID-19

The pathophysiology of lung involvement in severe SARS-CoV-2 disease includes bilateral diffuse alveolar injury with formation of fibromyxoid exudates, sloughing of pneumocytes, hyaline membrane formation and neutrophil infiltration[53]. The mechanism appears to be a combination of both direct viral-mediated injury and host inflammatory response. Although there have been anecdotal reports of sudden respiratory worsening with the development of ARDS progressing within 12-24 h, its presentation is more often delayed and typically after a week of onset of symptoms, suggesting the role of immune response of the host.

Humidified oxygen *via* nasal cannula for non-severe pneumonia is a useful strategy as in any hypoxemia. However, further escalation of supplemental oxygen strategies needs modification in the setting of SARS-CoV-2 lung involvement. Dry venturi masks without humidification should be used to avoid aerosolization risk. In general, high-flow nasal cannula (HFNC) and non-invasive positive pressure ventilation should be avoided in patients with SARS-CoV-2 ARDS[54]. The evidence for this is still evolving and should be decided on a case-to-case basis. Because the ARDS in SARS-CoV-2 disease evolves rapidly, several patients may fail a non-invasive ventilation trial. Learning from the SARS epidemic, the use of bi-level positive airway pressure was evidently associated with infection risk to healthcare workers while HFNC was not[55]. Hence, it is preferable to offer early intubation in patients with SARS-CoV-2 ARDS, avoiding non-invasive ventilation. A recent WHO guideline supported the liberal use of non-invasive ventilation strategies provided there is good interface fitting with no air leak[8]. Rapid sequence intubation without using ambu bag with experienced intensivists may be the least

Table V. Antivirals for the management of coronavirus disease 2019 (COVID-19)

Clinical category of COVID-19	Specific/antiviral therapy
Mild	Symptomatic treatment
Moderate*	Tablet hydroxychloroquine 400 mg bd × 1 day followed by 200 mg bd × 10 days
Severe*	Tablet hydroxychloroquine 400 mg bd × 1 day followed by 200 mg bd × 2 wk Tablet lopinavir 400 mg/ritonavir 100 mg bd × 2 wk

*There is insufficient evidence for or against most of the drugs mentioned above and should preferably be used in discussion with the patients or the next of kin. May consider new antiviral agents such as remdesivir or immunomodulatory therapy such as toclizumab in the appropriate setting

Source: Refs 31, 35

Table VI. Precautionary measures for infection control among healthcare workers

Procedures	Precautionary measures
Examining or providing care for patients	Surgical mask, goggles or face shield, gown/apron and gloves
Performing AGPs* on patients	N95 respiratory masks, goggles or face shield, gown and gloves

*Aerosol generating procedures (AGPs) include endotracheal intubation, non-invasive ventilation such as BiPAP, manual ventilation before intubation with ambu bag, administration of nebulized medications, disconnecting a ventilator, positioning prone of a ventilated patient, tracheostomy, bronchoscopy, open suctioning of intubated patients and cardiopulmonary resuscitation. BiPAP, bilevel positive airway pressure

Source: Ref. 63

aerosol inducing. Bundle approaches planned by the ICU teams can protocolize the aspects of ventilation for SARS-CoV-2 patients[56]. Early consideration of prone ventilation in patients with severe ARDS may prove beneficial.

Cardiovascular and shock management in SARS-CoV-2 disease

Acute cardiac injury (ACI) diagnosed by elevated troponins or abnormal ECG findings is commonly encountered in severe SARS-CoV-2 disease. Up to one-fifth of the hospitalized patients show ACI, typically late into disease onset with prognostic significance[57]. The mechanism of cardiac injury is not clear, but direct viral-mediated mechanisms appear less likely as autopsy studies have not shown evidence of the same[58]. In view of ACE-2 receptor attachment by SARS-CoV-2 virus and significant association with severe influenza disease, myocardial infarctions are also deemed to be higher in severe disease[59].

A significant proportion of critically ill SARS-CoV-2 patients develop shock during the hospital stay[60]. The common causes of this include cardiogenic shock, secondary infections, sepsis as well as cytokine storm. In patients with cytokine storm, cytokine blockade therapies such as IL-6 blockers may be beneficial in a select group of patients[61]. Early recognition of a secondary infection leading to septic shock, followed by initial resuscitation with crystalloids and then continuation with vasopressors administered through a central line, is recommended. Fluid overloading should be avoided. In the event of signs of poor perfusion and cardiac dysfunction persisting despite treatment with intravenous fluids and vasopressors with target blood pressure attained, ionotropic agents such as dobutamine may be considered[8].

Infection control in SARS-CoV-2

The predominant mode of person-to-person transmission in SARS-CoV-2 infection is by close contact with infected individuals generating respiratory droplets. The virus is capable of staying active on inanimate surfaces for several hours, making fomite transmission likely[62]. Airborne transmission though possible, does not appear to be a major mechanism[62]. This has particular implications due to shortage of personal protective equipment in various settings. Aerosol-generating procedures may generate smaller particles which may stay in the air for a longer time. Distant spread of such particles to produce secondary infection seems unlikely[63]. Table VI presents the safety measures for infection control to be followed among healthcare professionals.

Conclusion

Tackling the evolving COVID-19 pandemic requires a multifaceted approach. The government, health sector, community as well as each individual have a key role to play in the prevention of transmission of infection. Healthcare professionals should be trained in the clinical management of this rapidly spreading viral illness to enable them to swiftly and confidently detect and treat all infected individuals. It is of paramount importance that healthcare professionals are actively involved in infection control and provided adequate personal protective equipment to safeguard not only themselves but those surrounding them as well.

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