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Clinical Update on COVID-19

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Abstract

The rapid spread of severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) in Wuhan, China prompted an increased surveillance in India since early January 2020. The first laboratory confirmed case of COVID-19 in India was reported from Kerala on 30th January 2020. Since then the novel coronavirus infected pneumonia (NCIP) cases have been presenting to the hospital emergencies as severe acute respiratory illness (SARI) or influenza like illness (ILI). As on 4th June, 2020, about 2,10,000 confirmed cases have been detected in India with around 6,100 reported deaths. The major mode of transmission has been via close contact with infected individuals through respiratory droplets and fomites. The clinical spectrum varies from asymptomatic to mildly symptomatic (fever, myalgia, and sore throat) to acute respiratory distress syndrome as a part of cytokine release syndrome. The diagnosis depends on nucleic acid detection by rRT-PCR for SARS-CoV-2, IgM/IgG antibodies detection and typical radiological appearance in high suspects. Social distancing, isolation precautions, and proper hand hygiene with good cough etiquettes are all very important infection prevention and control (IPC) measures in mitigating the spread of the contagion. Repurposing of old and existing drugs like hydroxychloroquine, lopinavir/ritonavir, favipiravir, remdesivir, interferons have been found to be useful in various trials. Role of convalescent plasma and anti-inflammatory/immune-suppressive therapy is also being tried to some effect in cases with cytokine release syndrome. Personal protective equipments form a crucial part of the management of the affected individuals. Vaccine development and trials are being pursued with aggressive vigor worldwide.

Key words : COVID-19, SARS-CoV-2, COVID-19 therapy, COVID-19 pneumonitis, novel coronavirus, 2019-nCoV outbreak, pandemic.

Introduction

On 11 March 2020, the World Health Organisation (WHO) declared severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) as a pandemic that causes novel coronavirus disease 2019 (COVID-19)[1]. As on 4th June 2020, there have been 6.4 million confirmed cases from over 216 countries worldwide with almost 3,83,000 deaths. India has reported 2,10,000 cases with 6,100 deaths[2]. SARS-CoV-2 is a novel strain of betacoronavirus that has not been previously identified in humans. Phylogenetic analysis suggests that SARS-CoV-2 might have emerged from the zoonotic cycle and rapidly spread by human to human transmission[3]. However, the exact source of SARS-CoV-2 has not been identified yet. Transmission among humans occurs via close contact with an infected individual that produces respiratory droplets while coughing or sneezing within a range of about 2 metres[4]. COVID-19 as an emerging disease has unique pathophysiological characteristics, clinical manifestations, and radiological features. Although very challenging, yet considerable progress has been made on the clinical management aspect of this diseases as the information is being gathered and shared worldwide. This article will summarise the epidemiological, aetiological, clinical, pathological, and radiological characteristics of COVID-19 and review the latest advancements in the treatment.

Epidemiology of COVID-19

The epidemic curves reflect that the current epidemic may be a mixed outbreak pattern with initial cases suggestive of a continuous common source, potentially at Huanan seafood market in Hubei province of Wuhan, China; and later cases suggestive of a propagated source as the virus began to be transmitted from person to person. A phase-adjusted estimation of epidemic dynamics assumed that the effective reproduction number R_0 was 3.1 at the early phase of the epidemic[5]. Despite more than 1.5 million international arrivals to India from January 18 to March 23, India had tested only 5,900 individuals for SARS-CoV-2 up until 13th March, 2020. Since then, testing has been increased, but it has still not reached the desired level of coverage, both in terms of areas as well as numbers. To study the extent of spread of COVID-19 cases, ICMR tested for SARS-CoV-2 in samples from patients admitted with severe acute respiratory illness (SARI) in multiple centres spread across India from Feb 15 to Apr 2, 2020. In this study they estimated a conservative number of possible COVID-19 cases to be 1.8%[6]. SARS-CoV-2 spreads mainly through respiratory droplets or close contact. While in the later stage of infection, the virus is also detectable in anal swabs, suggesting the possibility of oral-faecal route transmission[7]. Significant environmental contamination by patients

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carrying SARS-CoV-2 through respiratory droplets and faecal shedding suggests that the environment serves as a potential medium of transmission and supports the requirement for strict adherence to environmental and hand hygiene[8]. The possibility of SARS-CoV-2 vertical transmission is still controversial. Literature reporting evidence of vertical transmission is limited. Luisa Patane *et al* in one study have described SARS-CoV-2 RNA on the foetal side of the placenta in two cases of mothers infected with COVID-19 and with neonates also positive for the virus at birth[9]. These findings support the possibility of vertical transmission of SARS-CoV-2 from the mother to the baby in-utero. Moreover, the direct visualisation of SARS-CoV-2 RNA in the infected placentas raises the possibility of estimating the viral load in cells with morphological context. In a study of 77 well-characterised infector-infectee pairs in Hong Kong, it was estimated that the serial interval (duration between symptom onset of a primary case to symptom onset of its secondary case) of COVID-19 was 5.8 days (mean), with 7.6% of serial intervals distributed negatively (i.e., the infectee developed symptoms prior to infector), strongly implying pre-symptomatic transmission[10]. Assuming a median incubation period of 5.2 days (based on other studies), the study estimated that the infectious period of SARS-CoV-2 started 2.3 days before onset of symptoms, peaking at 0.7 days and declining within 7 days.

SARS-CoV-2 genome and pathogenesis

SARS-CoV-2 is a single-stranded RNA virus of ~30 kb genome size, which belongs to the genus coronavirus and family Coronaviridae. Six other kinds of coronaviruses are known to cause human disease, including severe acute respiratory syndrome coronavirus (SARS-CoV) and middle east respiratory syndrome coronavirus (MERS-CoV) with high mortality rate. According to the genome characteristics, coronavirus is separated into four genera: α-CoV, β-CoV, γ-CoV and δ-CoV. Genomic sequencing revealed that the novel coronavirus isolated from lower respiratory tract samples of patients with COVID-19 belongs to β-CoV. The genome of SARS-CoV-2 is similar to other coronaviruses and comprises of ten open reading frames (ORFs)[11]. Coronavirus has the appearance of crown under electron microscopy and thus the name. They are enveloped viruses with a single-strand, positive-sense RNA genome, which is the largest known genome for a RNA virus. All coronaviruses share the same genome organisation and expression pattern, with two large overlapping reading frames (ORF1a/b) which encode 16 nonstructural proteins, followed by ORFs for four major

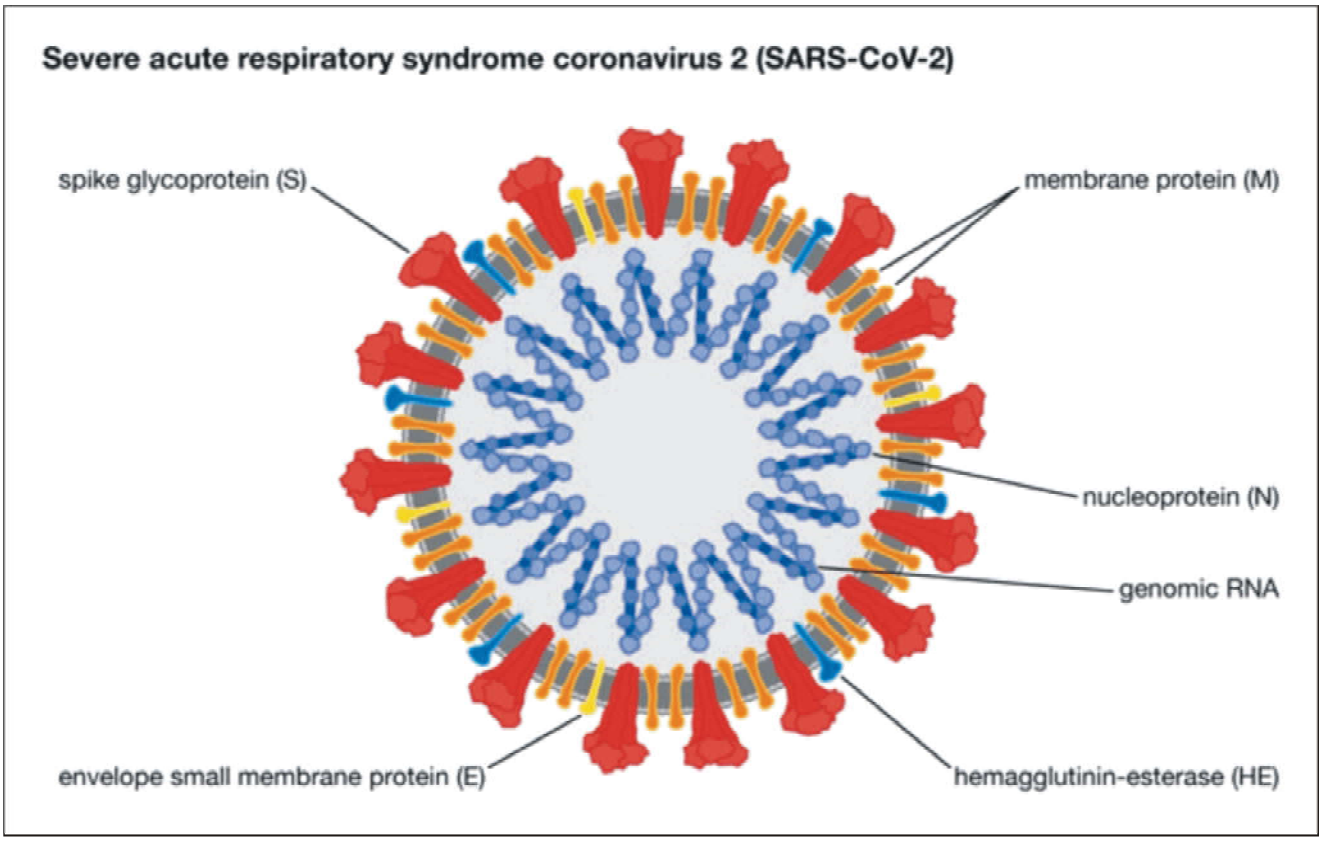
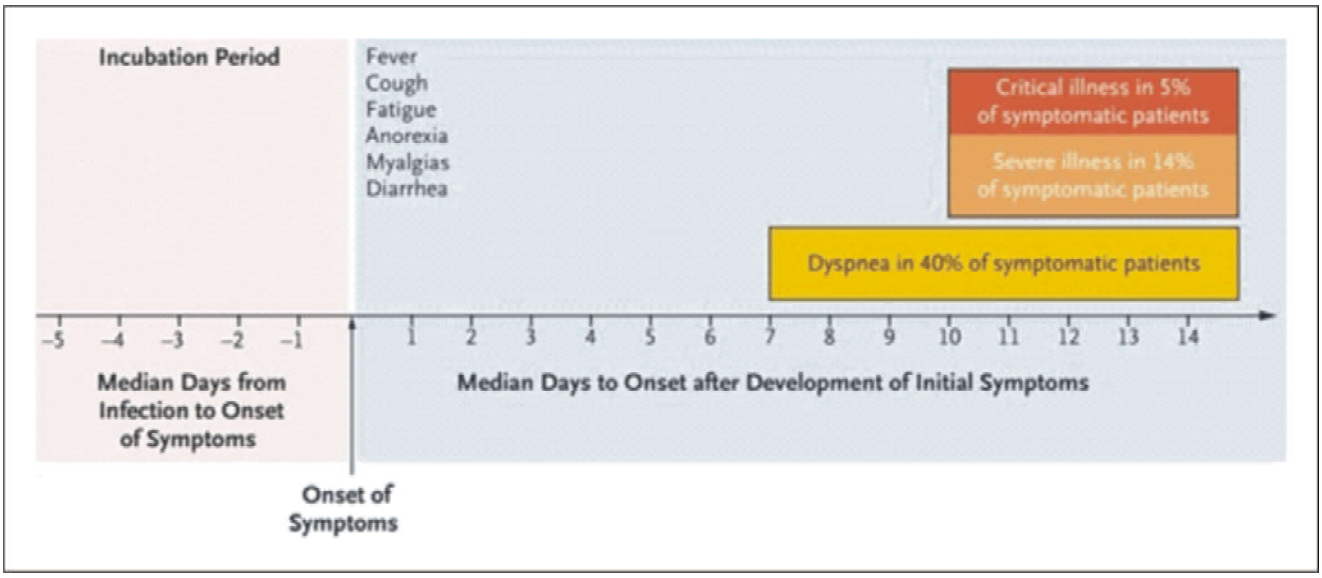


Fig. 1: *Schematic diagram of SARS-CoV-2 viral structure.*

structural proteins: spike (S), envelope (E), membrane (M), and nucleocapsid (N) (Fig. 1). Spike-protein plays an essential role in binding to receptors and is critical for determining host tropism and transmission capacity. It is functionally divided into S1 and S2 domain, responsible for receptor binding and cell membrane fusion, respectively. The receptor binding domain of β-CoV is commonly located in the C-terminal domain of S1. SARS-CoV-2 spike protein has 10- to 20-fold higher binding affinity to human angiotensin-converting enzyme 2 (ACE2) than SARS-CoV. Like SARS-CoV, SARS-CoV-2 uses the ACE2 receptor for internalisation and TMPRSS2 serine proteases for S protein priming[12]. Upon entry into the host target cells, the viral antigens get presented via antigen presenting cells (APCs) to virus-specific cytotoxic T lymphocytes (CTL). Studies have been conducted in SARS-CoV-2 infected patients showing the activation and reduction in CD4+ and CD8+ T cell counts. In addition, SARS-CoV-2 patients have been found to present with acute respiratory distress syndrome (ARDS). ARDS is a cytokine release syndrome (CRS) which is a lethal uncontrollable inflammatory response resulting from the release of large pro-inflammatory cytokines (IL-1β, IFN-α, IFN-γ, IL-12, IL-6, IL-18, TNF-α, IL-33, TGFβ, etc.) and chemokines (CCL3, CCL2, CXCL8, CCL5, CXCL9, CXCL10, etc.) by immune cells. The main protagonist of this storm is interleukin-6 (IL-6). IL-6 is produced mostly by activated leukocytes and acts on a large number of cells and tissues. It is able to promote the differentiation of B-lymphocytes. It also stimulates the production of acute-phase proteins and plays an important role in thermoregulation, bone maintenance and in the functionality of the central nervous system. Histopathological investigation of tissues from SARS-CoV-2 infected patients showed virus-induced cytopathic effect with signs of acute respiratory distress syndrome in both type-I and type-II pneumocytes[13].

Clinical manifestations

COVID-19 has an incubation period of 2 - 14 days, mostly ranging from 3 to 7 days. The clinical spectrum of COVID-19 varies from asymptomatic or pauci-symptomatic forms to clinical conditions characterised by respiratory failure that necessitates mechanical ventilation and support in an ICU, to multiorgan and systemic manifestations in terms of sepsis, septic shock, and multiple organ dysfunction syndromes (MODS) (Fig. 2). In one of the first reports on the disease, Huang *et al* illustrated that patients (n 41) suffered from fever, malaise, dry cough, and dyspnoea. Chest computerised tomography (CT) scans showed pneumonia with abnormal findings in all cases. About a third of those (n 13) required ICU care, and there were 6 (15%) fatalities[14]. As per the CDC list, the symptoms include – fever (85%), dry cough (86%), fatigue (44-70%), anorexia (40 - 84%), sputum production, shortness of breath (80%), sore throat, headache, myalgia/arthralgia (11 - 35%), chills or repeated shaking with chills, nausea or vomiting (24%), nasal congestion, new onset anosmia or dysgeusia, diarrhoea (27%), haemoptysis, conjunctival congestion[15]. Silent hypoxaemia has been a very talked about and commonly observed feature of COVID-19 in which the patient has low blood oxygen saturation level on pulse oximetry but is not apparently dyspnoeic. It is considered to be a clinical manifestation of underlying capillary



(Adapted from Zhou et al, and the Centers for Diseases Control and Prevention).

Fig. 2: *Timeline of symptoms of Severe coronavirus disease 2019 (COVID-19).*

dysfunction or thrombosis.

The authors of the Chinese CDC report divided the clinical manifestations of the disease by severity[5]:

- Mild disease: No pneumonia or mild pneumonia; occurred in 81% of cases.
- Severe disease: Dyspnoea, respiratory frequency ≥ 30/min, blood oxygen saturation (SpO2) ≤ 93%, PaO2/FiO2 ratio or P/F [the ratio between the blood pressure of the oxygen (partial pressure of oxygen, PaO2) and the percentage of oxygen supplied (fraction of inspired oxygen, FiO2)] < 300, and/or lung infiltrates > 50% within 24 to 48 hours; occurred in 14% of cases.
- Critical disease: Respiratory failure, septic shock, and/or multiple organ dysfunction (MOD) or failure (MOF); occurred in 5% of cases.

As per the WHO, COVID-19 disease severity is classified as:[16]–

Mild disease		Symptomatic patients meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia.
Moderate disease	**Pneumonia**	**Adolescent or adult** with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including SpO2 ≥ 90% on room air.
Severe disease	**Severe pneumonia**	**Adolescent or adult** with clinical of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or SpO2 < 90% on room air.
Critical disease	**ARDS**	As per Berlin definition.
	Septic Shock	As per sepsis-3 guidelines.

As a reference, the criteria for the severity of respiratory insufficiency as in Berlin definition of ARDS and the diagnostic criteria of sepsis and septic shock as in sepsis-3 guidelines, is followed to describe the disease severity in COVID-19. The risk factors for developing into severe to critical cases include advanced age (> 60 years), pregnancy, underlying comorbidities such as hypertension, diabetes, cardiovascular disease, chronic kidney diseases, malignancy, pre-existing pulmonary disease, immunosuppression, cerebrovascular disease and obesity[14].

Coagulopathy and thrombocytopenia are also common complications for COVID-19 infection, which increase the risk of haemorrhage and thrombosis. Mottled skin, petechial or purpuric rash, appearance of melena or haematuria is found in some cases. Patients with the syndrome of persistent hypoxaemia, chest pain, pre-syncope or syncope and haemoptysis should be suspected of having pulmonary thromboembolism (PTE)[17]. The manifestation of limb pain, swelling, erythema and dilated superficial veins should be suspected of deep vein thrombosis (DVT). Nearly 20% of patients have abnormal coagulation function, and most of severe and critical patients present with coagulation disorders and have the tendency to develop into disseminated intravascular coagulation (DIC)[14]. It may be hypothesised that myocardial injury is a result of microthrombus formation in the myocardial vasculature in the setting of a hypercoagulable state like DIC. Numerous studies have reported acute cardiac injury as an important manifestation of COVID-19[18]. AKI is primarily seen in COVID-19 patients with respiratory failure, with 89.7% of patients on mechanical ventilation developing AKI compared to 21.7% of non-ventilated patients. Risk factors for AKI included older age, diabetes mellitus, cardiovascular disease, black race, hypertension and need for ventilation and vasopressor medications. AKI occurs early and in temporal association with respiratory failure and is associated with a poor prognosis[19]. Mechanisms of renal injury have been hypothesised to include both acute tubular necrosis, direct cytotoxic effects of the virus itself and immune-mediated damage[20]. Neurologic manifestations are categorised into 3 categories: central nervous system (CNS) manifestations (dizziness, headache, impaired consciousness, acute cerebrovascular disease, ataxia, and seizure), peripheral nervous system (PNS) manifestations (taste impairment, smell impairment, vision impairment, and nerve pain) and skeletal muscular injury manifestations. Impaired consciousness includes the change of consciousness level (somnolence, stupor, and coma) and consciousness content (confusion and delirium)[21].

Laboratory investigations

Whom to test

Most countries are utilising some type of clinical and epidemiologic data to determine who should have testing performed. As per the Indian Council of Medical Research (ICMR) the following categories of individuals should be considered for COVID-19 testing in India:-

1. All symptomatic (ILI symptoms) individuals who have undertaken international travel in the last 14 days.
2. All symptomatic (ILI symptoms) contacts of laboratory confirmed cases.
3. All symptomatic healthcare personnel (HCP)/frontline workers involved in containment and mitigation of COVID-19.

4. All patients of Severe acute respiratory infection (SARI).
5. Asymptomatic direct and high risk contacts of a confirmed case to be tested once between day 5 and day 10 of coming into contact.
6. All symptomatic ILI within hotspots/containment zones.
7. All hospitalised patients who develop ILI symptoms.
8. All symptomatic ILI among returnees and migrants within 7 days of illness.
9. No emergency procedure (including deliveries) should be delayed for lack of test. However, sample can be sent for testing if indicated as above.

As per WHO guidelines:-

- ILI case is defined as one with acute respiratory infection with fever > 38° C AND cough.
- SARI case is defined as one with acute respiratory tract infection with fever > 38° C AND cough AND requiring hospitalisation.
- All testing in the above categories is recommended by real time RT-PCR test only.

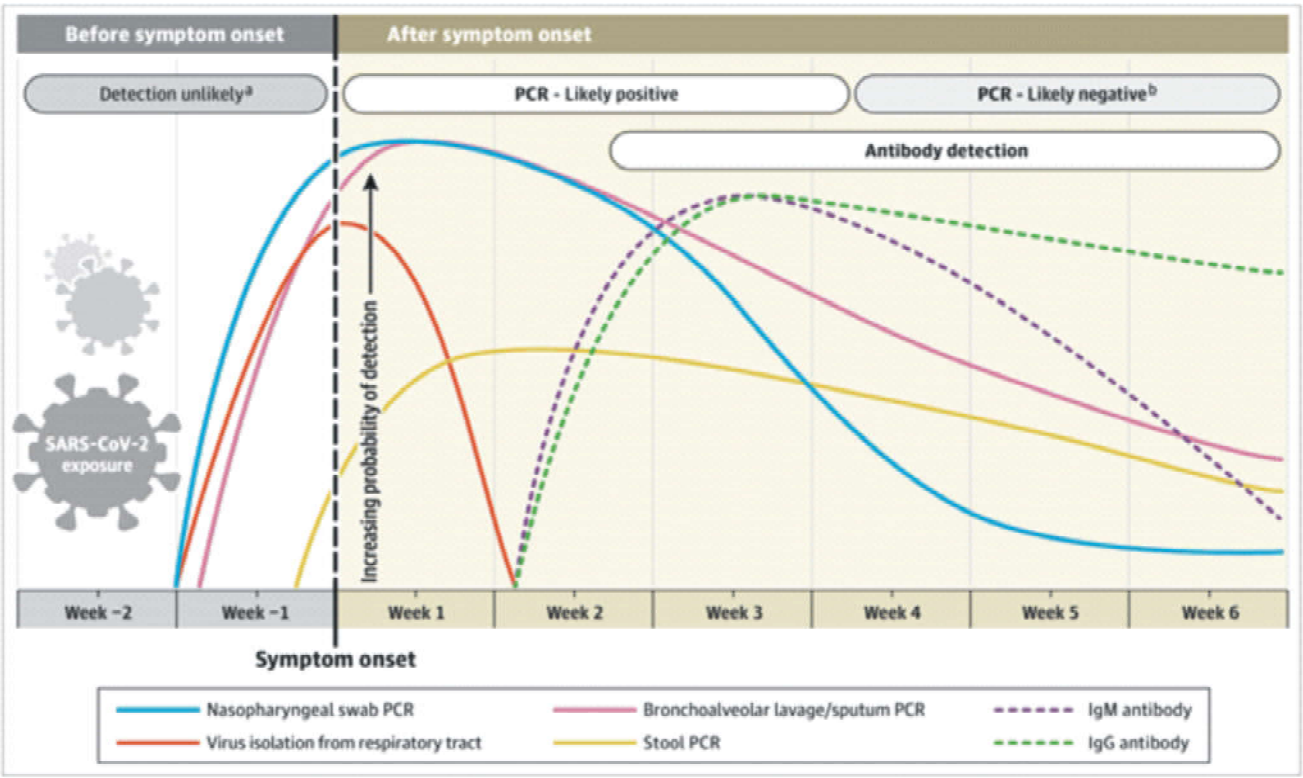
Case definitions (as per WHO)

Surveillance definition of suspect case: A person with acute respiratory infection (sudden onset of at least one of the following: fever, cough, sore throat, shortness of breath) requiring hospitalisation or not, *and*

In the 14 days prior to symptom onset, meets at least one of the following epidemiological criteria:

- Was in close contact with a confirmed or probable case of COVID-19, *or*

Figure. Estimated Variation Over Time in Diagnostic Tests for Detection of SARS-CoV-2 Infection Relative to Symptom Onset



Estimated time intervals and rates of viral detection are based on data from several published reports. Because of variability in values among studies, estimated time intervals should be considered approximations and the probability of detection of SARS-CoV-2 infection is presented qualitatively. SARS-CoV-2 indicates severe acute respiratory syndrome coronavirus 2; PCR, polymerase chain reaction.

[a] Detection only occurs if patients are followed up proactively from the time of exposure.

[b] More likely to register a negative than a positive result by PCR of a nasopharyngeal swab.

Fig. 3: *Estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset.*

(Adapted from Sethuraman N, Jeremiah SS, Ryo A. Interpreting Diagnostic Tests for SARS-CoV-2. JAMA, May 6, 2020. doi:10.1001/jama.2020.8259).

- History of travel to areas with ongoing community transmission of SARS-CoV-2, *or*
- Worked in or attended a healthcare facility where COVID-19 patients were being treated.

Probable case: A suspected case in whom testing for SARS-CoV-2 is inconclusive (result of the test reported by BSL4 lab) or in whom testing was positive on a pan-coronavirus assay.

Confirmed case: A person with laboratory confirmation of SARS-CoV-2 causing COVID-19 infection by rRT-PCR of oropharyngeal or nasopharyngeal swab, irrespective of clinical signs and symptoms.

Diagnosis

Molecular testing

The WHO recommends collecting specimens from both the upper respiratory tract (naso- and oropharyngeal samples) and lower respiratory tract such as expectorated sputum, endotracheal aspirate or bronchoalveolar lavage. The collection of BAL samples should only be performed in mechanically ventilated patients as lower respiratory tract samples seem to remain positive for a more extended period. Lower respiratory tract samples have a higher yield than upper respiratory tract samples, but often they are not obtained because of concerns about aerosolisation of virus during sample collection procedures. Laboratory confirmed COVID-19 patients are those who test positive on real-time reverse transcriptase polymerase chain reaction (rRT-PCR) of nasal and oropharyngeal swabs or sputum specimens. The collected clinical specimens are transported to designated laboratories in viral transport medium (VTM) and extraction of RNA is done, followed by rRT-PCR detection with primers and probes of appropriate sequences[14]. The value of cycle threshold (Ct) is the criterion to determine the detection result, with less than 37 being defined as negative, above 40 as positive and a medium load (37 - 40) calling for confirmation by retesting[22]. The estimated variation over time in diagnostic tests for detection of SARS-CoV-2 infection relative to symptom onset is shown in Fig. 3.

Serology testing

The detection of SARS-CoV-2 specific IgM and IgG antibodies can also be used for diagnosis but it is not recommended by the WHO for disease confirmation[23]. COVID-19 infection can be determined with one of the following criteria: positive specific IgM, the transformation of specific IgG from negative to positive, a 4-fold increase in IgG titre during recovery period compared with the result of acute phase. Although antibody detection is simple, rapid and inexpensive, it is still not widely used due to inherent limitations, like - false negativity resulting from the existence of a window period, limited sensitivity and specificity as compared with rRT-PCR, and absence of exclusion criteria, which makes it an epidemiological tool for sero-surveillance only.

Laboratory parameters

A majority of COVID-19 patients show normal leucocyte count and nearly one-third have leucopenia. Lymphocytopenia, as one of the most typical laboratory abnormalities, is present in 83.2% of patients[24]. Interestingly, lymphocytopenia appears to be a negative prognostic factor. The elevated neutrophil-to-lymphocyte ratio (NLR), derived NLR ratio (d-NLR) (neutrophil count divided by the result of WBC count minus neutrophil count), and platelet-to-lymphocyte ratio, can be the expression of the inflammatory storm[24]. The correction of these indices is an expression of a favourable trend. Many patients have liver function abnormalities with elevated alanine aminotransferase (ALT), aspartate aminotransferase (AST), and LDH. Liver damage in mild cases of COVID-19 is often transient and can return to normal without any special treatment. A prominent finding of SARS-CoV-2 is disarray of the coagulation and fibrinolytic system, with > 70% of non-survivors meeting criteria for disseminated intravascular coagulation (DIC)[25]. Hospitalised patients with moderate and severe COVID-19 and those with poorer outcomes are noted to have prolonged prothrombin time, elevated D-dimer and deranged activated partial thromboplastin time. Acute cardiac injury is variably defined as either cardiac troponin elevation > 99th percentile alone or a composite of troponin elevation, electrocardiographic, or echocardiographic abnormalities[18]. One of the more intriguing mechanisms for systemic injury in severe COVID-19 patients stems from the significant systemic inflammatory response. Many reports have demonstrated severely elevated levels of inflammatory biomarkers and cytokines, including IL-6, CRP, TNF-a, IL-2R, and ferritin[26]. Higher levels of these biomarkers are associated with more severe COVID-19 manifestations, known as cytokine release syndrome or cytokine storm, and worse outcomes. Acute kidney injury is also very common and is manifested as deranged urea, creatinine and decreased urine output.

Radiological features

Radiological images play an important role in the diagnosis and providing guidance for treatment. Standard radiographic examination (X-ray) of the chest has a low sensitivity in identifying early lung changes and in the initial stages of the disease. At this stage, it can be completely negative. In the more advanced stages of infection, the

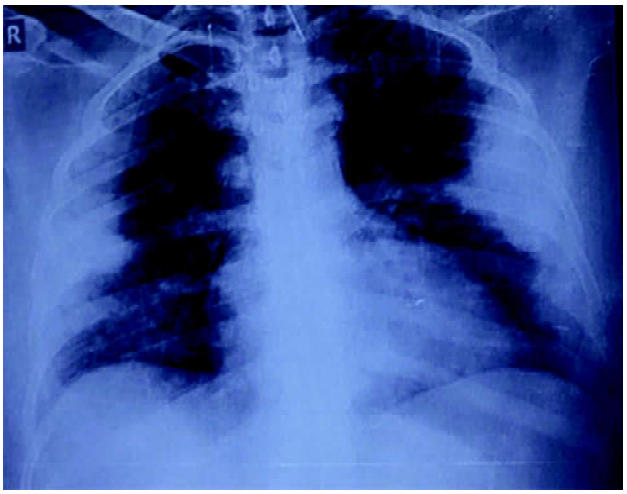


Fig. 4a: *Bilateral subpleural interstitial opacities.*

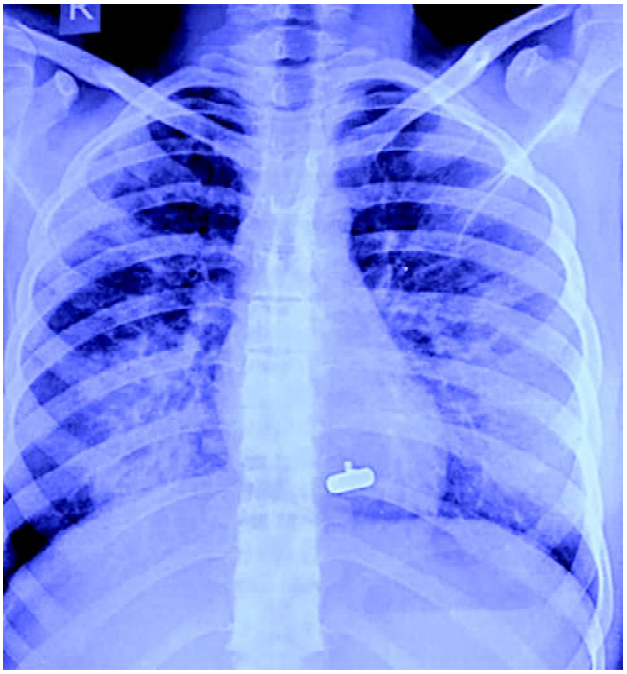


Fig. 4b: *Bilateral lower zone alveolar-interstitial infiltrates.*

Fig. 4 (a and b): *Some typical chest radiographs from confirmed COVID-19 cases.*

chest X-ray examination generally shows bilateral multifocal alveolar-interstitial opacities (Fig. 4a and 4b), which tend to confluence up to the complete opacity of the lung. Patients of varying severity presented significantly different lesions on chest CT imaging. Patients with mild disease manifested with unilateral and focal ground-glass opacities (GGOs) which gradually developed to bilateral or multilobular lesions. As the disease progressed further, GGOs evolved to consolidation lesions, presenting with mixed pattern or pure consolidation, with the latter being more common in critically ill patients admitted to ICU[27]. Consistent with the interstitial involvement in viral pneumonia, Zhao *et al* suggested that 48.5% of CT images manifested reticular patterns and 28.7% presented interlobular septal thickening[28]. Unlike influenza pneumonia, which usually exhibited unilateral GGOs and significant solid nodules, only 6% of COVID-19 patients had solid nodules. Moreover, other lesions included adjacent pleura thickening, vascular enlargement, bronchial wall thickening, traction bronchiectasis, air bronchogram, pericardial effusion, etc. During disease deterioration, increased number of or enlarged lesions could be observed in radiological imaging, and part of them even develop into a "white lung" with diffusely involved lung[29].

Broadly, COVID-19 pneumonitis has been divided into two primary phenotypes; L-type and H-type, although evidence is limited as of now[30].

COVID-19 pneumonia, type L

This group of patients presents with the following characteristics:-

- Low elastance : Nearly normal compliance.
- Low ventilation to perfusion (VA/Q) ratio: Hypoxaemia may be best explained by the loss of regulation of perfusion and by loss of vasoconstriction.
- Low lung weight. Only ground-glass densities are present on CT scan, primarily located subpleurally and along the lung fissures.
- Low lung recruitability. The amount of non-aerated tissue is very low.

COVID-19 pneumonia, type H (typical ARDS like picture)

- High elastance.
- High right-to-left shunt.
- High lung weight.

Lung ultrasound

Ultrasound approach can allow evaluating the evolution of the disease, from a focal interstitial pattern up to "white lung" with evidence often of subpleural consolidation. It should be performed within the first 24 hours in the suspect and every 24 to 48 hours and can be useful for patient follow-up, choice of the setting of mechanical ventilation and for indication of prone positioning. The main sonographic features are:-

- Pleural lines: Often thickened, irregular, and discontinuous until it almost appears continuous;

subpleural lesions can be seen as small patchy consolidations or nodules.

- B lines: They are often motionless, coalescent and can cascade and follow-up to the square of "white lung".
- Thickenings: They are most evident in the posterior and bilateral fields especially in the lower fields; the dynamic air bronchogram within the consolidation is a manifestation of disease evolution.
- Perilesional pleural effusion.

Clinical management

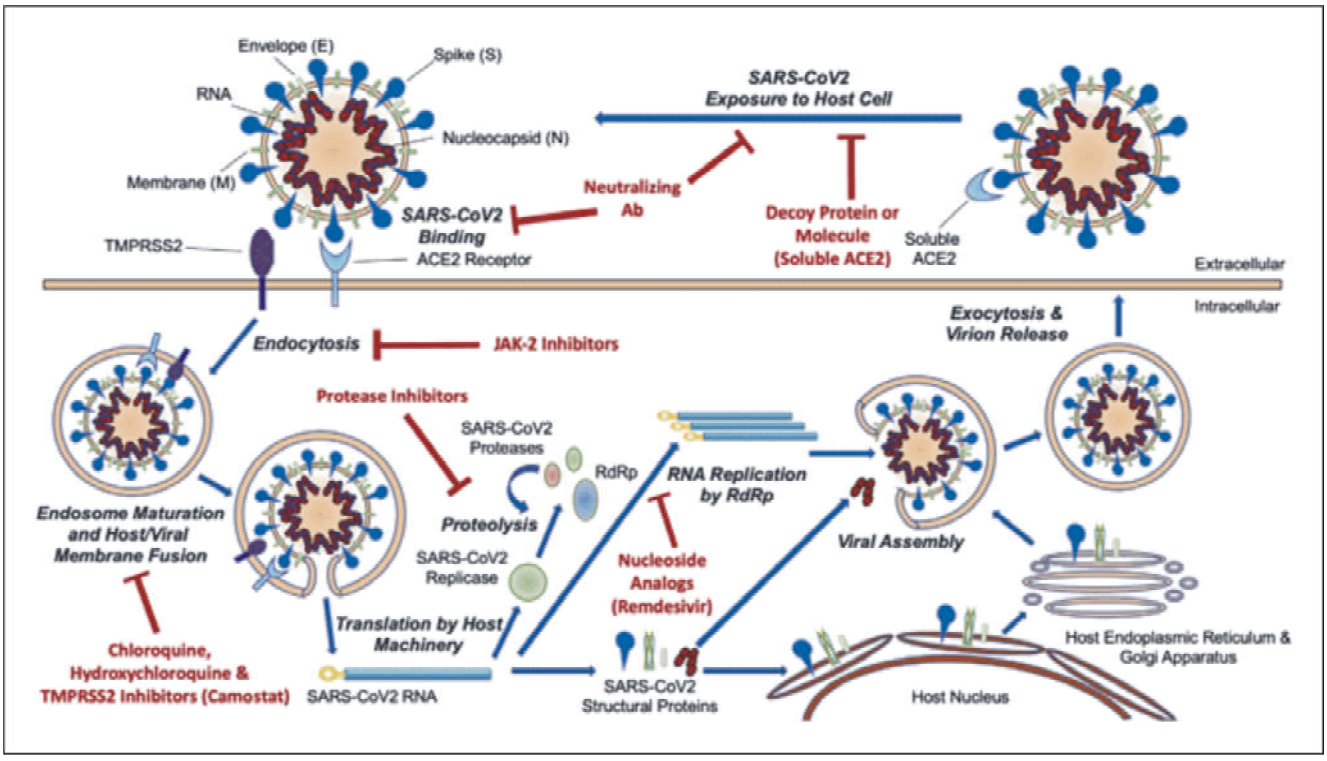
Infection prevention and control (IPC) measures

Preventive measures are the current strategy to limit the spread of cases because an epidemic will continue to propagate as long as R_0 is greater than 1. Control measures must focus on reducing the value to less than 1.

Preventive strategies are focussed on the isolation of patients and careful infection control, including appropriate measures to be adopted during the diagnosis and the provision of clinical care to an infected patient. For instance, droplet, contact and airborne precautions should be adopted during specimen collection, and sputum induction should be avoided.

The WHO and other organisations have issued the following general recommendations:-

- Avoid close contact with subjects suffering from acute respiratory infections.
- Wash your hands frequently, especially after contact with infected people or their environment.
- Avoid unprotected contact with farm or wild animals.
- People with symptoms of acute airway infection should keep their distance, cover coughs or sneezes with disposable tissues or clothes and wash their hands.



Severe Acute Respiratory Syndrome-CoronaVirus-2 (SARS-CoV-2) binds to the angiotensin-converting enzyme 2 (ACE2) receptor on the host cell membrane. Endocytosis is believed to be mediated, in part, by JAK-2. Membrane fusion occurs between the mature endosome and virion with facilitation by the transmembrane serine protease 2 (TMPRSS2) resulting in release of the SARS-CoV-2 RNA into the intracellular space. The RNA is translated by host machinery to produce the replicase and structural proteins. Host and SARS-CoV-2 proteases cleave the replicase into nonstructural proteins, including the RNA-dependent RNA polymerase (RdRp). RdRp mediates SARS-CoV-2 RNA replication and amplification. SARS-CoV-2 transmembrane proteins (spike [S], envelope [E], and membrane [M]) are shuttled via the endoplasmic reticulum and Golgi apparatus to the forming viral capsids. Viral assembly occurs with addition of the viral RNA and nucleocapsid (N) protein through association with the transmembrane viral proteins. Exocytosis results in release of the newly synthesised viral particle. Ab - antibody.

Fig. 5: *Putative SARS-CoV-2 life cycle and therapeutic targets.*

(Adapted from Atri et al. COVID-19 for the cardiologist. JACC: Basic to Translational Science 2020; 5 (5): 518-36).

- Strengthen – particularly in emergency medicine departments – the application of strict hygiene measures for the prevention and control of infections.
- Individuals that are immunocompromised should avoid public gatherings.

Healthcare workers caring for infected individuals should utilise contact and airborne precautions to include PPE such as N95 or FFP2/3 masks, eye protection, gowns, and gloves to prevent transmission of the pathogen.

Potential targeted or disease-modifying treatments in COVID-19

These is no specific antiviral treatment which has been proven to be effective for COVID-19. Combinations of over three antivirals are not suggested. Current treatment options are mainly based on previous experience showing clinical benefits in treating influenza, ebola, MERS, SARS, and other viral infections. The preceding review of the viral physiology of SARS-CoV-2 and the various potential mechanisms of injury to the host serve as the basis for considering specific targeted treatment and prevention (Fig. 5).

Antiviral therapy

Nucleoside analogs: inhibitors of viral genome replication (remdesivir, favipiravir)

The antiviral mechanism of nucleoside analogs is to interfere with RdRp (RNA dependent RNA polymerase) function and viral genome replication and amplification. The most widely applied agent in this class against SARS-CoV-2 has been remdesivir. Remdesivir functions as a chain terminator of RNA replication, initially designed for use against Ebola[31]. Addition of remdesivir to the growing RNA strand by RdRp, blocks the incorporation of additional nucleosides, thereby halting genome replication. The agent has been shown to have in vitro activity against SARS-CoV-2, leading to off-label and investigational use around the world[32]. Multiple randomised control trials are ongoing in China and the United States for moderate, severe, and critical COVID-19. Another nucleoside analog for the disruption of RdRp-dependent viral replication is favipiravir, which has investigational approval in several countries[33]. Additional agents that are under study include emtricitabine or tenofovir and ribavirin[33].

Protease inhibitors: inhibitors of nonstructural protein generation (lopinavir/ritonavir)

The antiviral mechanism of action of protease inhibitors is to block viral proteases that cleave the nonstructural proteins from the large, monomeric replicase. As the maturation of nonstructural proteins, such as RdRp, is necessary for viral reproduction, the pharmacologic impairment of the protease might be effective to stop viral replication. A randomised control trial of lopinavir-ritonavir, a combination protease inhibitor designed for human immunodeficiency virus treatment, in 199 patients with at least moderate COVID-19 did not significantly alter clinical improvement or viral clearance[34]. Other candidate protease inhibitors for SARS-CoV-2 include danoprevir, a drug originally intended for hepatitis C therapy[33].

Inhibitors of membrane fusion

For the viral genome to access the host cellular machinery for replication, a membrane fusion event must occur between the viral and endosomal membranes, which are non-covalently bound by the interaction between the S protein and ACE2. The exact mechanism of membrane fusion is not known but appears to be dependent on endosomal maturation and a membrane-bound host protease, TMPRSS2[35].

Chloroquine and hydroxychloroquine

Chloroquine (CQ) and hydroxychloroquine (HCQ) are thought to inhibit endosomal maturation, a process by which endosomes are translocated from the perimembrane regions of the cell to central hubs. CQ prevented viral replication of SARS-CoV-1 *in vitro*[36]. A follow-up study demonstrated comparable efficacy of HCQ, a less toxic derivative, and suggested that the mechanism of impaired endosomal maturation applied to SARS-CoV-2 infection *in vitro*[37]. Only poor quality, non-randomised, unblinded data exist assessing the benefit of HCQ in COVID-19. Although HCQ is being widely used, more data is needed to prove efficacy against SARS-CoV-2 in humans. Notably, CQ and HCQ prolong the QT_C interval and may induce arrhythmia; significant caution should be used in starting these agents in patients with a QT_C interval > 500 ms. Concomitant use of other QT_C prolonging agents is not recommended.

Camostat

Camostat is a protease inhibitor approved for the treatment of chronic pancreatitis. Camostat appears to inhibit TMPRSS2 in proteomic and *in vitro* studies[35]. A randomised, placebo-control trial is underway for this agent in COVID-19 in the US.

Neutralising antibodies/convalescent plasma and decoy proteins

Neutralising antibodies are designed to bind virions, preventing viral exposure or binding to host cells. Plasma

from patients who have recovered from SARS-CoV-2 may contain anti SARS-CoV-2 IgG antibodies. In a small, single-arm trial of convalescent plasma in COVID-19 patients with ARDS, all had clinical improvement, with 3 of 5 patients weaned off the ventilator[38]. Additional trials are ongoing to better define the safety and efficacy of this strategy.

Isolation of SARS-CoV-2 specific neutralising antibodies with clonal techniques is an appealing strategy to provide targeted therapy, potentially with lower risk of adverse events. Strategies currently under investigation include antibodies cloned from convalescent serum of individuals recovered from SARS-CoV-2 or SARS-CoV-1 and synthetic antibodies. It is unclear whether differences in the S proteins of SARS-CoV-1 and SARS-CoV-2 may limit the effectiveness of antibodies cloned from patients convalescent to SARS-CoV-1[39]. Synthetic antibodies represent an exciting, novel therapeutic avenue. One strategy being explored is to fuse ACE2 to fragment crystallisable region immunoglobulin G, with the hypothesis that this synthetic antibody would serve as a decoy receptor, preventing cellular binding of the virion[40]. Few studies are ongoing of decoy proteins that are designed to act as viral "sinks". There is preliminary success with this strategy using soluble human ACE2[41].

Anti-inflammatory therapy

Advanced stages of COVID-19 have been likened to cytokine storm syndromes with nonspecific widespread immune activation. Elevated levels of inflammatory biomarkers, such as IL-6 and hsCRP, identify patients at high risk of progressing to severe disease and death. Immunomodulatory and anti-inflammatory therapy have been used, despite limited data, in patients with evidence of hyperinflammation in an effort to curb pathologic immune activation.

Corticosteroids

Corticosteroids have been used in several, severe viral respiratory infections including influenza, SARS-CoV, and MERS-CoV with limited benefit and, in some instances, evidence of delayed viral clearance and increased rates of secondary infection and mortality. A retrospective analysis of 84 patients with ARDS secondary to SARS-CoV-2 observed an association with improved survival in patients who received solumedrol[42]. In the absence of robust evidence, major professional society guidelines do not recommend routine use of corticosteroids in treatment of COVID-19 but rather restricting its use to patients with other indications for steroids, such as refractory shock or advanced ARDS[43].

Interleukin-6 (IL-6) inhibitors

Elevation of IL-6 in patients with severe COVID-19 has prompted consideration of use of IL-6 inhibitors (tocilizumab, siltuximab) extrapolating from treatment of cytokine release syndrome[44]. Tociluzimab, a recombinant humanised monoclonal antibody, and siltuximab, a chimeric monoclonal antibody, both bind soluble and membrane bound IL-6 receptors resulting in inhibition of IL-6 mediated signaling. In one case series from China, 21 patients with severe or critical COVID-19 treated with tocilizumab experienced a salutary effect with resolution of fever, improved oxygenation, improvement in lung opacities on chest computed tomography, resolution of lymphopenia and a reduction in CRP levels within a few days of therapy in the absence of any significant reported adverse events[45].

Azithromycin

Azithromycin, a macrolide antibiotic, has long been touted for its anti-inflammatory effect and has been used as adjunctive therapy in treatment of community acquired pneumonia and chronic obstructive pulmonary disease exacerbations. A small nonrandomised study showed that combination azithromycin and HCQ was associated with more effective SARS-CoV-2 clearance in COVID-19 patients compared with either monotherapy with HCQ or standard of care; however, numerous limitations of this study render the data uninterpretable[46]. QT_C interval monitoring is important, especially when used in combination with HCQ.

Other anti-inflammatory therapies

JAK-2 inhibitors inhibit receptor mediated-endocytosis, leading to the hypothesis that it might prevent cellular entry of the SARS-CoV-2. Additionally, this class of agents have anti-inflammatory effects by inhibiting cytokine release. An agent in the class, baricitinib, is being studied in an open-label non-randomised pilot study in patients with COVID-19[47]. Currently, a 3-arm randomised control trial is being launched to compare anakinra monotherapy, emapalumab monotherapy, and standard of care. Anakinra is a recombinant monoclonal antibody that blocks IL-1 receptors. It has been used to treat autoimmune conditions including juvenile idiopathic arthritis as well as recurrent pericarditis. Emapalumab is a human anti interferon-gamma monoclonal antibody that has been approved for treatment of primary haemophagocytic lymphohistiocytosis, a disease reminiscent of the hyperinflammatory state seen in advanced COVID-19. Finally, colchicine, a microtubule polymerisation inhibitor and anti-inflammatory drug, is being tested in large randomised clinical trial of ambulatory COVID-19 patients.

Vaccine development

As the discovery of a safe and efficacious vaccine again

SARS-CoV-2 is clearly the aspiration for preventative strategies, intense efforts are ongoing employing numerous approaches with accelerated testing. It is believed that all 4 structural proteins (E, M, N, and S) may serve as antigens for neutralising antibody and $CD4^+$ $CD8^+$ T-cell responses. Encouragingly, administration of full length of the ACE2 receptor-binding domain of the S protein of SARS-CoV-1 induced highly potent neutralising antibodies that conveyed protective immunity in animal models. Potential delivery strategies include inactivated or attenuated virus, subunit vaccines, viral vectors, and DNA- or RNA-based vaccines[49].

Other supportive therapy

Anticoagulation

In clinical practice, nearly 20% of patients with COVID-19 are found to have abnormal coagulation function and almost all severely and critically ill patients presented coagulation disorders. Anticoagulation should be given with great caution in patients with DIC although microthrombosis has been observed in lung, liver, and other organs on autopsy of COVID-19 patients. Ishan Paranjpe and Valentin Fuster *et al*, analysed the association between in-hospital anticoagulation administration and mortality among patients hospitalised with COVID-19. Of the 2,773 hospitalised COVID-19 patients, 786 (28%) received systemic anticoagulation during their hospital stay. Patients who received anticoagulation were more likely to require mechanical ventilation. Longer duration of anticoagulation treatment was associated with a reduced mortality risk[48]. According to the researchers, anticoagulation may be associated with improved outcomes in COVID-19 patients, but the benefits should be weighed against the risk of bleeding. Also, heparins bind tightly to SARS-CoV-2 spike proteins and also downregulate IL-6, thus directly dampening the immune hyperactivation.

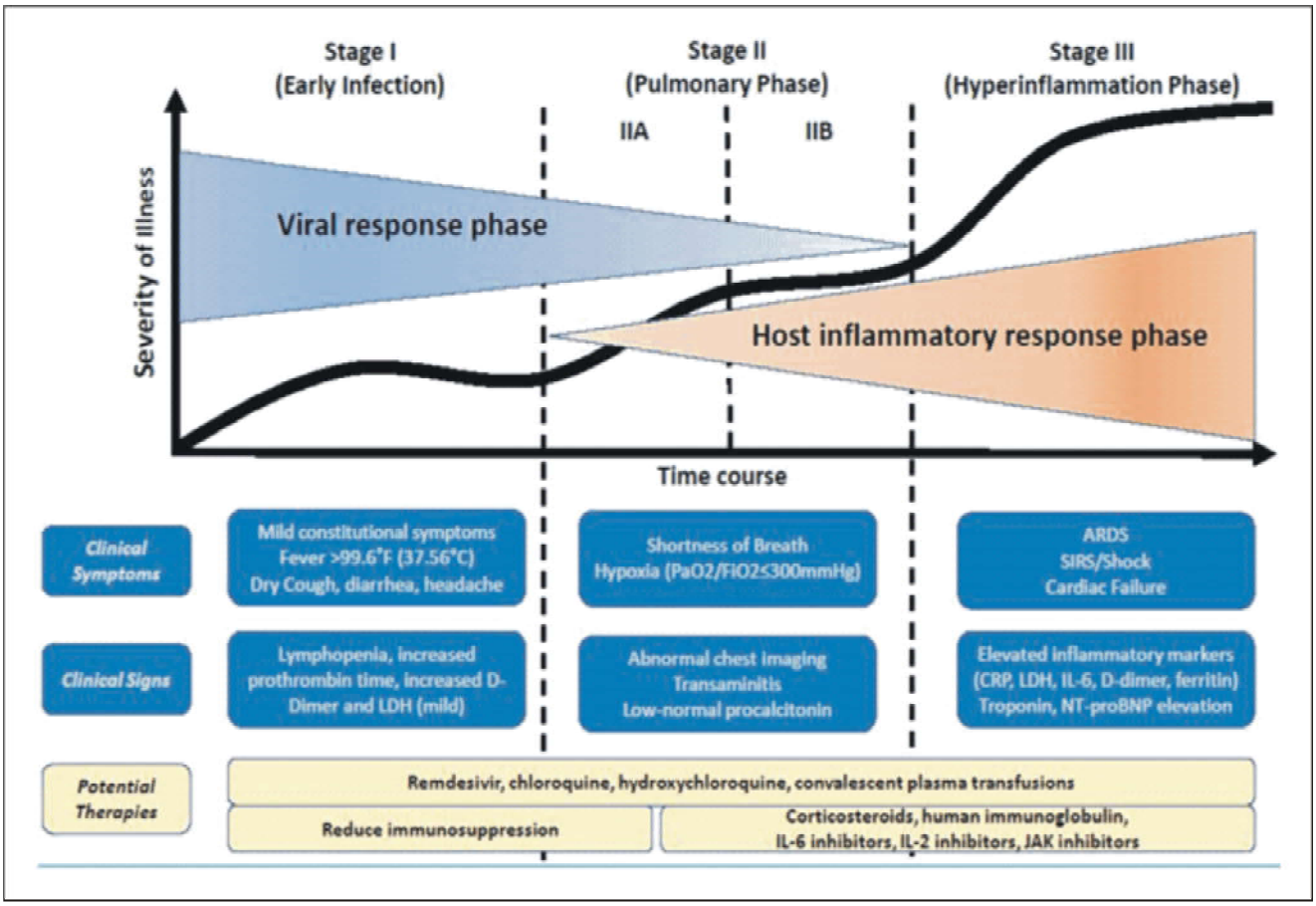


Fig. 6: *Classification of COVID-19 disease states and potential therapeutic targets. Legend: The figure shows three escalating phases of disease progression with COVID-19, with associated signs, symptoms, and potential phase-specific therapies. ARDS = Acute respiratory distress syndrome; CRP = C-reactive protein; IL = Interleukin; JAK = Janus kinase; LDH = Lactate dehydrogenase; SIRS = Systemic inflammatory response syndrome.*

(Adapted from Siddiqi HK et al. COVID-19 illness in native and immunosuppressed states: A clinical-therapeutic staging proposal. J Heart Lung Transplant, 2020).

Oxygen therapy and mechanical ventilation

For mild-to-moderate patients with hypoxaemia, nasal catheters and non-rebreather or venturi masks and even high-flow nasal cannula oxygen therapy (HFNC) are advised. While for severe and critical patients with respiratory distress, HFNC, non-invasive mechanical ventilation (NIV) with helmet mask or invasive mechanical ventilation, and even ECMO should be considered. Nebulisation therapy should be avoided in COVID-19 wards for risk of aerosol generation and spread.

HFNC (> 50 l/min) can provide accurate oxygen concentration and a certain positive airway pressure to promote alveolar expansion to improve oxygenation and respiratory distress. However, according to expert consensus on the use of HFNC for COVID-19, patients with cardiac arrest, weak spontaneous breathing, PaO_2/FiO_2 < 100 mmHg, $PaCo_2$ > 45 mmHg and pH < 7.25 and upper airway obstruction are contraindicated.

For severe patients with respiratory distress or hypoxaemia that cannot be alleviated after standard oxygen therapy, NIV can also be considered with close surveillance. It is important that appropriate fit masks or helmet masks should be used to mitigate aerosol spread.

Invasive ventilation should be done in case NIV fails to improve respiratory parameters within 1 - 2 hours trial. Endotracheal intubation should be performed by a trained and experienced provider using airborne precautions. Patients with ARDS, especially young individuals or those who are obese or pregnant, may de-saturate quickly during intubation. Pre-oxygenate with 100% FiO_2 for 5 minutes, via a face mask with a reservoir bag, bag-valve mask, HFNO, or NIV. Rapid sequence intubation is appropriate after an airway assessment that identifies no signs of difficult intubation. Implement mechanical ventilation using lower tidal volumes (4 - 8 ml/kg predicted body weight, PBW) and lower inspiratory pressures (plateau pressure < 30 cm of H_2O). Prone positioning and even ECMO might be required in refractory hypoxaemia even on invasive ventilation.

Antimicrobial therapy

Empiric antimicrobial therapy should be instituted in all severe COVID-19 patients within one hour of presentation, covering all usually encountered microbes as per the local ecological data of the microbiological flora. All relevant culture specimens especially paired blood culture samples should be obtained prior to first dose of antibiotic administration. De-escalation of therapy should be done as soon as the culture results are available.

Conclusion and future perspective

In this review, we have presented an overview of the epidemiological, aetiological, clinical, pathological, and imaging characteristics of COVID-19 and given a brief overview of the latest advancements in the treatment. As it is a new entity with a widely varying clinical disease spectrum, management poses a big challenge to all the treating clinicians. At the same time, therapeutic protocols need to be revised as per the rapidly evolving understanding of the disease. It is like building the ship while sailing. The treatment should be customised for every individual after assessing the clinical status and pathophysiologic phase of the disease spectrum (Fig. 6). The COVID-19 pandemic can cause short-term fiscal distress and longer-term damage to the global economic growth. A joint global cohesive effort is required in order to contain this pandemic. It is notable that in the present pandemic scenario, innovative artificial intelligence (AI) — powered surveillance, quick and strategic response actions — the trinity of testing-isolation-contact tracing, committed social distancing measures travel restrictions, self-isolation, implementation of personal and public hygiene, and extensive mobilisation of medical care facilities are helping the world mitigate through. For preventing future outbreaks of SARS-CoV-2 infection, high-volume cutting-edge investigations are warranted in understanding the COVID-19 pathology, CoV-2 origin, biology, structural data of potential surface antigens, and precise anti-CoV-2 antiviral therapies. Although the global economy is suffering at the hands of COVID-19, it is important to review the current action plans and suitably improvise the future action plans to avoid any potential recurrence.

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