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Review Article

A Review on Acute Respiratory Syndrome Corona Virus 2 (SARS-Cov-2) & Its Preventive Management

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A B S T R A C T

At the end of 2019 a novel virus, severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), causing severe acute respiratory syndrome expanded globally from Wuhan, China. In March 2020 the World Health Organization declared the SARS-Cov-2 virus a global pandemic. Severe Acute Respiratory Syndrome Coronavirus 2 can attack lung cells because there are many conserved receptor entries, namely Angiotensin Converting Enzyme-2. The presence of this virus in host cells will initiate various protective responses leading to pneumonia and Acute Respiratory Distress Syndrome. This review aimed to provide an overview related to this Corona Virus Disease 2019 (COVID-19) epidemiology, pathophysiology, diagnosis, management and future perspective. We searched PubMed, Medline, Embase and Scopus databases for Severe Acute Respiratory Syndrome Coronavirus-2, Middle East respiratory syndrome-related coronavirus and Severe Acute Respiratory Syndrome Coronavirus. Full texts were retrieved, analyzed and developed into an easy-to-understand review. Although only when the pandemic ends it will be possible to assess the full health, social and economic impact of this global disaster, this review represents a picture of the current state of the art. In particular, we focus on public health impact, pathophysiology and clinical manifestations, diagnosis, case management, emergency response and preparedness. The Ministry of Health and Family Welfare, Government of India and ICMR (Indian Council of Medical Research) has formulated guidelines, advisories for social distancing protocol, diagnosis, management, do's and don'ts and other reliable material.

Keywords: Coronavirus; COVID-19; Pathogenesis; Preparedness; Emergency; Pandemic

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INTRODUCTION:

The global pandemic of novel coronavirus disease 2019 (COVID-19) caused by severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) began in Wuhan, China, in December 2019 and was identified as a pandemic by the World Health Organization (WHO) on March 11, 2020 [1]. As of May 30, 2020, more than 59 million people were confirmed to have been infected and tested positive for COVID-19, with over 367,166 deaths worldwide [2]. COVID-19 was first identified and isolated in the respiratory tract of patients with pneumonia in Wuhan, china [3, 4]. The virus was identified as a novel enveloped RNA betacoronavirus that has been named as Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) [5]. As on 31 May 2020, 08:00 IST there were 89,995 Active Cases, 86,983 Cured/ Discharged, 1 Migrated and 5,164 Deaths in India. Recovery rate has improved significantly with 47.40% amongst COVID-19 patients (on 30.05.20), an increase of 4.51% in the recovery rate from the previous day's recovery rate of 42.89%. (WHO) [2].

The Covid-19 is very similar in symptomatology to other viral respiratory infections. Cases vary from mild forms to severe ones that can lead to serious medical conditions or even death. It is believed that symptoms may appear in 2 to 14 days, as the incubation period for the novel coronavirus has not yet been confirmed [6]. Symptomatic transmission refers to transmission of SARS-CoV-2 from persons with symptoms. Epidemiology and virologic studies sugest that transmission mainly occurs from symptomatic people to others by close contact through respiratory droplets, by

direct contact with infected persons, or by contact with contaminated objects and surfaces [7]. Clinical and virologic studies that have collected repeated biological samples from confirmed patients demonstrate that shedding of SARS-CoV-2 is highest in the upper respiratory tract (URT) (nose and throat) early in the course of the disease [8], within the first 3 days from onset of symptoms [9]. The incubation period for COVID-19, which is the time between exposure to the virus (becoming infected) and symptom onset, is, on average, 5–6 days, but can be up to 14 days. During this period, also known as the "presymptomatic" period, some infected persons can be contagious, from 1–3 days before symptom onset [10]. It is important to recognize that presymptomatic transmission still requires the virus to be spread via infectious droplets or by direct or indirect contact with bodily fluids from an infected person. An asymptomatic case is a person infected with SARS-CoV-2 who does not develop symptoms.

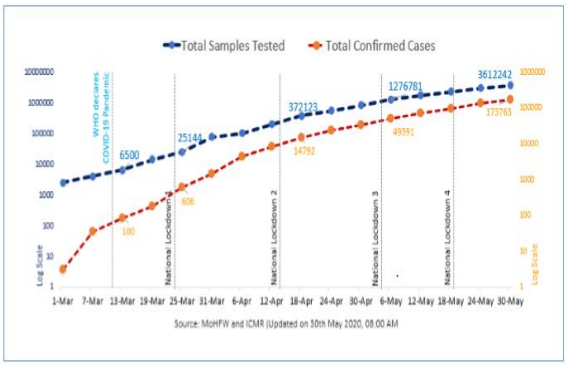


Figure: 1 Data source MOHFW and ICMR

While most people with COVID-19 develop only mild (40%) or moderate (40%) disease (see Table 2), approximately 15% develop severe disease that requires oxygen support, and 5% have critical disease with complications such as respiratory failure, acute respiratory distress syndrome (ARDS), sepsis and septic shock, thromboembolism, and/or multiorgan failure, including acute kidney injury and cardiac injury [10]. Older age, smoking [11] and underlying noncommunicable diseases (NCDs), such as diabetes, hypertension, cardiac disease, chronic lung disease and cancer, have been reported as risk factors for severe disease and death, and multivariable analyses have confirmed older age, higher sequential organ failure assessment (SOFA) score and D-dimer > 1 µg/L on admission were associated with higher mortality [12, 13] (see Table 2). This study also observed a median duration of viral RNA detection of 20.0 days (IQR 17.0–24.0) in survivors, but COVID-19 viral RNA was detectable until death in non-survivors. The longest observed duration of viral RNA detection in survivors was 37 days [12, 13].

COVID-19 is associated with mental and neurological manifestations, including delirium or encephalopathy, agitation, stroke, meningo-encephalitis, impaired sense of smell or taste [14] anxiety, depression and sleep problems. In many cases, neurological manifestations have been reported even without respiratory symptoms. Anxiety and depression appear to be common amongst people hospitalized for COVID-19, with one hospitalized cohort from Wuhan, China, revealing over 34% of people experiencing symptoms of anxiety and 28% experiencing symptoms of depression [15]. An observational case series from France found that 65% of people with COVID-19 in intensive care units (ICUs) showed signs of confusion (or delirium) and 69% experienced agitation [16]. Delirium, in particular, has been associated with increased mortality risk in the context of COVID-19 [17]. Moreover, there have been concerns related to acute cerebrovascular disease (including ischaemic and haemorrhagic stroke) in multiple case series from China, France, the Netherlands, and the United States of America [15,16,18,19]. Case reports of Guillain-Barré syndrome and meningo-encephalitis among people with COVID-19 have also been reported [20, 21].

Table: 1 Symptoms and risk factors associated with COVID-19

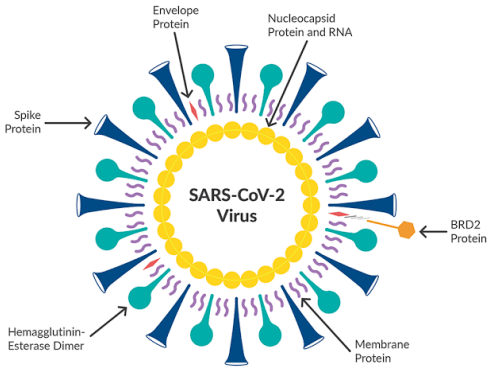
Clinical presentation	Presenting signs and symptoms of COVID-19 vary.
	Most persons experience fever (83–99%), cough (59–82%), fatigue (44–70%), anorexia (40–84%), shortness of breath (31–40%), myalgias (11–35%). Other non-specific symptoms, such as sore throat, nasal congestion, headache, diarrhoea, nausea and vomiting, have also been reported [12]. Loss of smell (anosmia) or loss of taste (ageusia) preceding the onset of respiratory symptoms has also been reported [14].
	Older people and immunosuppressed patients in particular may present with atypical symptoms such as fatigue, reduced alertness, reduced mobility, diarrhoea, loss of appetite, delirium, and absence of fever [22].
	Symptoms such as dyspnoea, fever, gastrointestinal (GI) symptoms or fatigue due to physiologic adaptations in pregnant women, adverse pregnancy events, or other diseases such as malaria, may overlap with symptoms of COVID-19 [23].
	Children might not have reported fever or cough as frequently as adults [23].
Risk factors for severe disease	Age more than 60 years (increasing with age).
	Underlying noncommunicable diseases (NCDs): diabetes, hypertension, cardiac disease, chronic lung disease, cerebrovascular disease, chronic kidney disease, immune suppression and cancer have been associated with higher mortality.
	Smoking

Table: 2 COVID-19 disease severity

Mild disease		Symptomatic patients (Table 1) meeting the case definition for COVID-19 without evidence of viral pneumonia or hypoxia. See the WHO website for most up-to-date case definitions [2].
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. Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast breathing and/or chest indrawing) and no signs of severe pneumonia. Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Severe disease	Severe pneumonia	Adolescent or adult with clinical signs 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. Child with clinical signs of pneumonia (cough or difficulty in breathing) + at least one of the following: • Central cyanosis or SpO2 < 90%; severe respiratory distress (e.g. fast breathing, grunting, very severe chest indrawing); general danger sign: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions [24]. • Fast breathing (in breaths/min): < 2 months: ≥ 60; 2–11 months: ≥ 50; 1–5 years: ≥ 40. While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.
Critical disease	Acute respiratory distress syndrome (ARDS)	**Onset:** within 1 week of a known clinical insult (i.e. pneumonia) or new or worsening respiratory symptoms. **Chest imaging:** (radiograph, CT scan, or lung ultrasound): bilateral opacities, not fully explained by volume overload, lobar or lung collapse, or nodules. **Origin of pulmonary infiltrates:** respiratory failure not fully explained by cardiac failure or fluid overload. Need objective assessment (e.g. echocardiography) to exclude hydrostatic cause of infiltrates/oedema if no risk factor present.
	Sepsis	**Adults:** acute life-threatening organ dysfunction caused by a dysregulated host response to suspected or proven infection. Signs of organ dysfunction include: altered mental status, difficult or fast breathing, low oxygen saturation, reduced urine output, fast heart rate, weak pulse, cold extremities or low blood pressure, skin mottling, laboratory evidence of coagulopathy, thrombocytopenia, acidosis, high lactate, or hyperbilirubinemia. **Children:** suspected or proven infection and ≥ 2 age-based systemic inflammatory response syndrome (SIRS) criteria,e of which one must be abnormal temperature or white blood cell count.
	Septic shock	**Adults:** persistent hypotension despite volume resuscitation, requiring vasopressors to maintain MAP ≥ 65 mmHg and serum lactate level > 2 mmol/L. **Children:** any hypotension (SBP < 5th centile or > 2 SD below normal for age) or two or three of the following: altered mental status; bradycardia or tachycardia (HR < 90 bpm or > 160 bpm in infants and heart rate < 70 bpm or > 150 bpm in children); prolonged capillary refill (> 2 sec) or weak pulse; fast breathing; mottled or cool skin or petechial or purpuric rash; high lactate; reduced urine output; hyperthermia or hypothermia [25, 26].

Origin and Structure of SARS-CoV2

A sample isolation from pneumonia patients who were some of the workers in the Wuhan seafood market found that strains of SARS-CoV-2 had a length of 29.9 kb [27]. Structurally, SARS-CoV-2 has four main structural proteins including spike (S) glycoprotein, small envelope (E) glycoprotein, membrane (M) glycoprotein, and nucleocapsid (N) protein, and also several accessory proteins [28]. The spike or S glycoprotein is a transmembrane protein with a molecular weight of about 150 kDa found in the outer portion of the virus. S protein forms homotrimers protruding in the viral surface and facilitates binding of envelope viruses to host cells by attraction with angiotensin-converting enzyme 2 (ACE2) expressed in lower respiratory tract cells. This glycoprotein is cleaved by the host cell furin-like protease into 2 subunits namely S1 and S2. Part S1 is responsible for the determination of the host virus range and cellular tropism with the receptor binding domain make-up while S2 functions to mediate virus fusion in transmitting host cells [29,30]. The nucleo capsid known as N protein is the structural component of CoV localizing in the endoplasmic reticulum-Golgi region that structurally is bound to the nucleic acid material of the virus. Because the protein is bound to RNA, the protein is involved in processes related to the viral genome, the viral replication cycle, and the cellular response of host cells to viral infections [31,32]. N protein is also heavily phosphorylated and suggested to lead to structural changes enhancing the affinity for viral RNA [29].



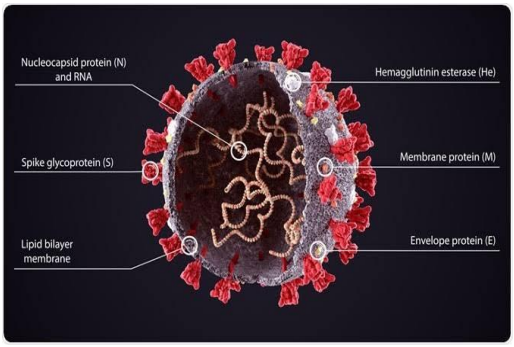


Figure: 2a. Schematic diagram of the SARS-CoV-2,

Figure 2b. Structure of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2)

Another important part of this virus is the membrane or M protein, which is the most structurally structured protein and plays a role in determining the shape of the virus envelope. This protein can bind to all other structural proteins. Binding with M protein helps to stabilize nucleocapsids or N proteins and promotes completion of viral assembly by stabilizing N protein-RNA complex, inside the internal virion. The last component is the envelope or E protein which is the smallest protein in the SARS-CoV structure that plays a role in the production and maturation of this virus [31].

In supporting the process of entry of the virus into the host cell, SARS-CoV2 binds to the ACE2 receiver that is highly expressed in the lower respiratory tract such as type II alveolar cells (AT2) of the lungs, upper esophagus and stratified epithelial cells, and other cells such as absorptive enterocytes from the ileum and colon, cholangiocytes, myocardial cells, kidney proximal tubule cells, and bladder urothelial cells [33]. Therefore, patients who are infected with this virus not only experience respiratory problems such as pneumonia leading to Acute Respiratory Distress Syndrome (ARDS), but also experience disorders of heart, kidneys, and digestive tract.

SARS-CoV-2:Virology and Drug Targets

SARS-CoV-2, a single-stranded RNA-enveloped virus, targets cells through the viral structural spike (S) protein that binds to the angiotensin-converting enzyme 2 (ACE2) receptor [34]. Following receptor binding, the virus particle uses host cell receptors and endosomes to enter cells. A host type 2 transmembrane serine protease, TMPRSS2, facilitates cell entry via the S protein [35]. Once inside the cell, viral polyproteins are synthesized that encode for there plicase-transcriptase complex. The virus then synthesizes RNA via its RNA-dependent RNA polymerase. Structural proteins are synthesized leading to completion of assembly and release of viral particles [36-38]. These viral life cycle steps provide potential targets for drug therapy (Figure). Promising drug targets include non structural proteins (e.g., 3-chymotrypsin-likeprotease, papain like protease, RNA-dependent RNA polymerase), which share homology with other novel coronaviruses (nCoVs). Additional drug targets include viral entry and immune regulation pathways [39,40].

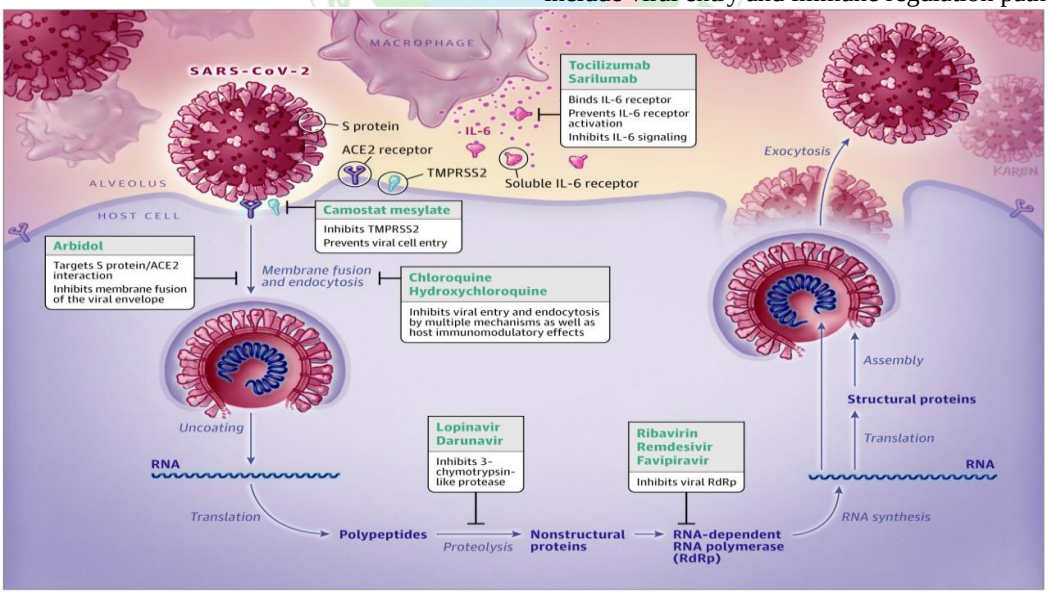


Figure: 3 Simplified Representation of Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) Viral Lifecycle and Potential Drug Targets

Pathophysiology and Clinical Manifestation

The pathogenetic mechanisms of SARS-CoV-2, its viral structure and genome must be considered. Coronaviruses are enveloped positive strand RNA viruses with the largest known RNA genomes-30-32 kb-with a 50-cap structure and 30-poly-A tail. Starting from the viral RNA, the synthesis of polyprotein 1a/1ab (pp1a/pp1ab) in the host is realized [41]. The transcription works through the replication-transcription complex (RCT) organized in double-membrane vesicles and via the synthesis of subgenomic RNAs (sgRNAs) sequences. Of note, transcription termination occurs at transcription regulatory sequences, located between the so-called open reading frames (ORFs) that work as templates for the production of sub genomic

mRNAs [42]. In the atypical CoV genome, atleast six ORFs can be present. Among these, a frame shift between ORF1a and ORF1b guides the production of both pp1a and pp1ab polypeptides that are processed by virally encoded chymotrypsin-likeprotease (3CLpro) or main protease (Mpro), as well as one or two papain-like proteases for producing 16 non-structural proteins (nsps) [42]. Apart from ORF1a and ORF1b, other ORFs encode for structural proteins, including spike, membrane, envelope, and nucleocapsid proteins and accessory proteic chains [41,42]. Different CoVs present special structural and accessory proteins translated by dedicated sgRNAs. Pathophysiology and virulence mechanisms of CoVs, and therefore also of SARS-CoV-2 have links to the function of the nsps and structural proteins. For instance, research has underlined that nsps are able to block the host innate immune response [43]. Among the functions of the structural proteins, the envelope has a crucial role in virus pathogenicity as it promotes viral assembly and release.

The pathogenic mechanism that produces pneumonia seems to be particularly complex [44] . The data so far available seem to indicate that the viral infection is capable of producing an excessive immune reaction in the host. In some cases, a reaction takes place, which as a whole is labelled a "cytokine storm". The effect is extensive tissue damage. The protagonist of this storm is interleukin 6 (IL-6). IL-6 is produced by activated leukocytes and acts on a large number of cells and tissues [45]. It is able to promote the differentiation of B lymphocytes, promotes the growth of some categories of cells, and inhibits the growth of others. It also stimulates the production of acute phase proteins and plays an important role in thermoregulation, in bone maintenance and in the functionality of the central nervous system [46]. Although the main role played by IL-6 is pro-inflammatory, it can also have anti-inflammatory effects. In turn, IL-6 increases during inflammatory diseases, infections, autoimmune disorders, cardiovascular diseases and some types of cancer [47]. It is also implicated into the pathogenesis of the cytokine release syndrome (CRS) that is an acute systemic inflammatory syndrome characterized by fever and multiple organ dysfunction [48]. The virus might pass through the mucous membranes, especially nasal and larynx mucosa, then enters the lungs through the respiratory tract. Then the virus would attack the targeting organs that express angiotensin converting enzyme 2 (ACE2), such as the lungs, heart, renal system and gastrointestinal tract [46-48]. The virus begins a second attack, causing the patient's condition to aggravate around 7 to 14 days after onset. B lymphocyte reduction may occur early in the disease, which may affect antibody production in the patient. Besides, the inflammatory factors associated with diseases mainly containing IL-6 were significantly increased, which also contributed to the aggravation of the disease around 2 to 10 days after onset. The clinical spectrum of COVID-19 varies from asymptomatic or paucisymptomatic forms to clinical conditions characterized by severe respiratory failure that necessitates mechanical ventilation and support in an intensive care unit (ICU), to multi organ and systemic manifestations in terms of sepsis, septicshock and multiple organ dysfunction syndromes (MODS) [49]. Pneumonia appears to be the most frequent serious manifestation of clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness [50]. There are no specific clinical features that can yet reliably distinguish COVID-19 from other viral respiratory infections. Other, less common symptoms have included headaches, sore throat, and rhinorrhea. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. In addition to respiratory symptoms, gastro intestinal symptoms (e.g., nausea and diarrhea) have also been reported and in some patients they may be the presenting complaint. Respiratory droplet transmission is the main route and it can also be transmitted through person-to-person contacts by asymptomatic carriers [49-50].

Diagnosis

A confirmed case is a suspect case with a positive molecular test. Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/ sputum/ endotracheal aspirates and bronchoalveolar lavage). Virus may also be detected in the stool and in severe cases, the blood. It must be remembered that the multiplex PCR panels currently available donot include the COVID-19. Commercial tests are also not available at present. In a suspect case in India, the appropriate sample has to be sent to designated reference labs in India or the National Institute of Virology in Pune. As the epidemic progresses, commercial tests will become available. Other laboratory investigations are usually non specific. The white cell count is usually normal or low. There may be lymphopenia; a lymphocyte count <1000 has been associated with severe disease. The platelet count is usually normal or mildly low. The CRP and ESR are generally elevated but procalcitonin levels are usually normal. A high procalcitonin level may indicate a bacterial co-infection. The ALT/AST, prothrombin time, creatinine, D-dimer, CPK and LDH may be elevated and high levels are associated with severe disease. The chest X-ray (CXR) usually shows bilateral infiltrates but may be normal in early disease. The CT is more sensitive and specific. CT imaging generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients/ patients with no clinical evidence of lower respiratory tract involvement. In fact, abnormal CTscans have been used to diagnose COVID-19 in suspect cases with negative molecular diagnosis; many of these patients had positive molecular tests on repeat testing [51, 52].

Treatment & Management

There is no specific antiviral treatment recommended for COVID-19, and no vaccine is currently available [53]. The treatment is symptomatic, and oxygen therapy represents the major treatment intervention for patients with severe infection. Mechanical ventilation may be necessary in cases of respiratory failure refractory to oxygen therapy, whereas hemodynamic support is essential for managing septic shock [53]. Different strategies can be used depending on the severity of the patient and local epidemiology [54, 55]. Outpatients with COVID-19 should stay at home and try to separate themselves from other people in the household. They should wear a face mask when in the same room (or vehicle) as other people and when presenting to health care settings. Disinfection of frequently touched surfaces is also important. The optimal duration of home isolation is uncertain, but in consideration of incubation time around 14 days without symptoms (fever, dyspnoea, others) are considered sufficient to end home isolation. Some patients with suspected or documented COVID-19 have severe

disease that warrants hospital care. Management of such patients consists of ensuring appropriate infection control, and supportive care. Patients with severe disease often need oxygenation support. High-flow oxygen and noninvasive positive pressure ventilation have been used. Some patients may develop acute respiratory distress syndrome and warrant intubation with mechanical ventilation; extracorporeal membrane oxygenation may be indicated in patients with refractory hypoxia.

The main pharmacological experimental options are as Glucocorticoids should not be used in patients with COVID-19 pneumonia unless there are other indications (e.g., exacerbation of chronic obstructive pulmonary disease) [56, 57]. Glucocorticoids have been associated with an increased risk for mortality in patients with influenza and delayed viral clearance in patients with Middle East respiratory syndrome coronavirus (MERS-CoV) infection. Although they were widely used in management of severe acute respiratory syndrome (SARS), there was no good evidence for benefit, and there was persuasive evidence of adverse short- and long-term harm [58, 59]. A number of investigational agents are being explored for antiviral treatment of COVID-19, and enrolment in clinical trials should be discussed with patients or their proxies. Certain investigational agents have been described in observational studies or are being used anecdotally based on in vitro or extrapolated evidence as Arbidol, Cemostate mesylate, Chloroquine and hydroxychloroquine, Lopinavir, Darunavir, Ribavirin, Remdesivir, Fevipiravir, Tocilizumab etc.

Umifenovir (also known as Arbidol) is a more promising repurposed antiviral agent with a unique mechanism of action targeting the S protein/ACE2 interaction and inhibiting membrane fusion of the viral envelope [60]. The agent is currently approved in Russia and China for the treatment and prophylaxis of influenza and is of increasing interest for treating COVID-19 based on invitro data suggesting activity against SARS. This observational data can not establish the efficacy of umifenovir for COVID-19, but ongoing RCTs in China are further evaluating this agent.

Camostat mesylate, an approved agent in Japan for the treat ment of pancreatitis, prevents nCoV cell entry invitro through inhibition of the host serine protease, TMPRSS2[61]. This novel mechanism provides an additional drug target for future research. SARS-CoV-2 uses the ACE2 receptor for entry into the host cell [61]. This discovery has stimulated discussions about whether ACE inhibitors and/or angiotens in receptor blockers may potentially treat COVID-19 These drugs up regulate ACE2 receptors, which could theoretically lead to worse outcomes if viral entry is enhanced[62].

Chloroquine and hydroxychloroquine have antiviral activity in vitro, as well as anti-inflammatory activities. Chloroquine and hydroxychloroquine appear to block viral entry into cells by inhibiting glycosylation of host receptors, proteolytic processing, and endosomal acidification [63] and on activity against many pro-inflammatory cytokines (e.g., IL-1 and IL-6) [64, 65]. Chloroquine phosphate and Hydroxychloroquine were reported in this review and showed favorable outcomes in the recovery of COVID-19 patients [66-71]. The mechanism of action on viruses for these two medicines is likely the same effect. Chloroquine has been used for a long time to treat malaria and showed positive outcomes in patients. Furthermore, Hydroxychloroquine showed a significant effectiveness to kill intracellar pathogens such as Coxiella burnetii, the agent of Q fever [72]. The French open label, non- randomized clinical trial was promising and the first clinical trial of these medications in COVID-19 patients. The effect of Hydroxychloroquine was significant because it showed reduction in the viral load when it compared with the control group [72]. Moreover, the effect of Hydroxychloroquine was significantly more potent when Azithromycin was added to the patients according to their clinical need. However, clinical follow-up and occurrence of adverse effects were not discussed in the paper; further work should be done on these medicines with the aim of reducing the morbidity and mortality of COVID-19 [68-70]. Although these two medicines have shown promising activity against SARSCoV-2, there is a risk of arrhythmia associated with their administration. Therefore caution is required for use at higher cumulative dosages. It is recommended that their use in suspected/confirmed COVID-19 is to be restricted to hospitalized patients. On March 30th, 2020 the U.S Food and Drug Administration (US FDA) has issued an emergency use authorization (EUA) for Chloroquine and Hydroxychloroquine to treat patients hospitalized with Covid-19 [71].

Lopinavir/ritonavir, a US Food and Drug Administration (FDA)- approved oral combination agent for treating HIV, demonstrated in vitro activity against other novel corona viruses via in hibition of 3-chymotrypsin-likeprotease [73, 74] and appears to have some activity against MERS-CoV in animal studies [75]. However, there was no difference in time to clinical improvement or mortality at 28 days in a randomized trial of 199 patients with severe COVID-19 given lopinavir-ritonavir (400/100 mg) twice daily for 14 days in addition to standard care versus those who received standard of care alone [76]. No published SARS-CoV-2 invitro data exist for lopinavir/ritonavir. [77] A systematic review of lopinavir / ritonavir for the treatment of SARS and MERS found limited available studies, with most of these investigating SARS.

Ribavirin, aguanine analogue, inhibits viral RNA-dependent RNA polymerase. Its activity against other nCoVs makes it a candidate for COVID-19 treatment. [78] No evidence exists for inhaled ribavirin for nCoV treatment, and data with respiratory syncytial virus suggest inhaled administration offers no benefit over intravenous administration. [79]

Remdesivir, formally known as GS-5734, is a novel nucleotide analogue monophosphate prodrug that undergoes metabolism to an active C-adenosine nucleoside tri phosphate analogue. Currently, remdesivir is a promising potential therapy for COVID-19 due to its broad-spectrum, potent in vitro activity against several nCoVs, including SARS-CoV-2 with EC50 and host polymerase selectivity against the Ebola virus[80]. The compassionate use of remdesivir through an investigational new drug application has been described in various studies [81, 82]. Any clinical impact of remdesivir on COVID-19 remains unknown.

Favipiravir, previously known as T-705, is a prodrug of a purine nucleotide, favipiravir ribofuranosyl-5′-triphosphate. The active agent inhibits the RNA polymerase, halting viral

replication. Most of favipiravir's preclinical data a rederived from its influenza and Ebola activity; however, the agent also demonstrated broad activity against other RNA viruses.[83] No published SARS-CoV-2 invitro data exist for favipiravir. Tocilizumab is a recombinant humanized monoclonal antibody which binds to the interleukin-6 (IL-6) receptor and blocks it from functioning. It is used for patients with severe COVID-19 and elevated IL-6 levels; the agent is being evaluated in a clinical trial [84].

Moreover, limited evidence are available for baraticinib, a numb-associated kinase (NAK) inhibitor, with a particularly high affinity for the kinase AAK1, apivotal regulator of clathrin-mediated endocytosis, anakinra, an anti IL-1, used in some UTI settings in Lombardy, Italy, and faviparavir a RNA-dependent RNA-polymerase inhibitor. Patients with hypercapnia, hemodynamic instability, multiorgan failure, or abnormal mental status should generally not receive HFNO, although emerging data suggest that HFNO may be safe in patients with mild-moderate and non-worsening hypercapnia [85, 86]. In positive patients with a D-Dimer value four times higher than the normal limit, and without anticoagulant contraindications, an anticoagulation therapy is recommended [87].

Interestingly, there is hypothesis of the link between angiotensin converting enzyme (ACE) inhibitors and COVID-19. Indeed, SARS-CoV-2 uses ACE receptor 2 for entry into target and in animal experiments both lisinopril and losartan can significantly increase mRNA expression of cardiac ACE2. If this were the case, we might be able to reduce the risk of fatal COVID-19 courses in many patients by temporarily replacing these drugs [88]. Existing literature strongly recommends that healthy patients continue therapy, and in hospitalized patients to modify ACE-I/ARB with other therapy.

Convalescent plasma treatment was mentioned once in this review, in a multi-centre cohort research trial of 45 critically ill COVID-19 patients admitted to ICU in Wuhan. The findings showed that convalescent plasma was administered to six patients and no transfusion reactions occurred; however, the study could not provide adequate information about the efficacy of convalescent plasma, due to limited sample sizes and lack of randomized control group [89-90].

In fact, convalescent plasma therapy could be a promising method of treatment for COVID-19 patients. A very recent case series reported from China, showed that five critically ill patients with laboratory confirmed COVID-19 (who had ARDS) improved. After receiving plasma transfusion, their body temperature normalized within 3 days (in 4 of 5 patients), their viral loads became undetectable within 12 days and 3 of 5 patients were discharged from the hospital and were in stable condition at 37 days post transfusion [91]. On March 24th, 2020 the US FDA has approved convalescent plasma treatment for investigational use under the traditional Investigational New Drug Applications (IND) regulatory pathway, and for eligible patients who have confirmed COVID-19 and severe or immediately life-threatening conditions such as respiratory failure, septic shock, and/or multiple organ dysfunction or failure [92-93].

Notably there are some potential risks and ethical issues associated with their use, including increased thrombotic event risk (0.04 to 14.9%), lack of high quality research in this particular area and the selection of donors with high neutralizing antibody titers [93].

Preventive measurements

Since at this time there are no approved treatments for this infection, prevention is crucial. Several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery. Isolation of confirmed or suspected cases with mild illness at home is recommended [51]. The ventilation at home should be good with sunlight to allow for destruction of virus. Patients should be asked to wear a simple surgical mask and practice cough hygiene. Caregivers should be asked to wear a surgical mask when in the same room as patient and use hand hygiene every 15–20 min. The greatest risk in COVID-19 is transmission to healthcare workers. It is important to protect healthcare workers to ensure continuity of care and to prevent transmission of infection to other patients. While COVID-19 transmits as a droplet pathogen and is placed in Category B of infectious agents (highly pathogenic H5N1 and SARS), by the China National Health Commission, infection control measures recommended are those for category A agents (cholera, plague). Patients should be placed in separate rooms or cohorted together. Negative pressure rooms are not generally needed. The rooms and surfaces and equipment should under go regular decontamination preferably with sodium hypochlorite. Healthcare workers should be provided with fit tested N95 respirators and protective suits and goggles. Airborne transmission precautions should be taken during aerosol generating procedures such as incubation, suction and tracheostomies. All contacts including healthcare workers should be monitored for development of symptoms of COVID-19. Patients can be discharged from isolation once they are a febrile for atleast 3 d and have two consecutive negative molecular tests at 1 d sampling interval. This recommendation is different from pandemic flu where patients were asked to resume work/school once a febrile for 24 hor by day 7 of illness. Negative molecular tests were not a prerequisite for discharge. At the community level, people should be asked to avoid crowded areas and postpone non-essential travel to places with ongoing transmission. They should be asked to practice cough hygiene by coughing in sleeve/tissue rather than hands and practice hand hygiene frequently every 15–20 min. Patients with respiratory symptoms should be asked to use surgical masks. The use of mask by healthy people in public places has not shown to protect against respiratory viral infections and is currently not recommended by WHO [94].

Ethical considerations that affect all persons affected by COVID-19

Equal moral respect: Every person is equally valuable. Treatment and care decisions should be based on medical need and not on irrelevant or discriminatory features such as ethnicity, religion, sex, age, disability or political affiliation. Patients with similar health problems or symptoms must receive equal treatment and care. Showing moral respect means involving patients and their caregivers

in decision-making to the greatest extent possible, explaining options and limitations in treatment.

Duty of care: Every patient is owed the best possible care and treatment available in the circumstances. Even when resources need to be rationed during a crisis, health care professionals and frontline workers have a duty of care to promote their patients' welfare within available resources. Health care professionals and frontline workers are also owed a duty of care. In this regard, appropriate PPE for health care professionals and frontline workers should be provided to promote their safety and well-being. This is a benefit to them but also to the whole of society by ensuring that they are available to support the clinical response for as long as possible.

Non-abandonment: It follows from consideration of equal moral respect and duty of care, that no person in need of medical care should ever be neglected or abandoned. Care will extend to families and friends of patients and options to maintain communication with them should be explored. Palliative care must be accessible for all patients with respiratory failure for whom ventilatory support will be withheld or withdrawn.

Protection of the community: Appropriate IPC should be in place, respected and enforced. Such actions protect patients, health care professionals and the community. During a pandemic the focus should be on both clinical care for patients and the promotion of public health.

Confidentiality: All communications between patient and clinician must remain confidential except in the case of compelling public health concerns (e.g. contact tracing and surveillance etc.) or other accepted justifications for breach of confidentiality. Private individual information must be kept secure unless it is a justified breach [95-96].

CONCLUSIONS

The current novel corona virus pandemic has challenged the economic, medical and public health infrastructure of India and of other countries. There have been rapid advances in what we know about the pathogen, how it infects cell and causes disease and clinical characteristics of disease. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Due to rapid transmission, countries around the world should increase attention into disease surveillance systems and scale up country readiness. Although further research is warranted as the amount of the evidence increases, this study presents the current picture of treatment modalities used for COVID-19. Efficacy and safety profiles of treatments for COVID-19 will need to be characterized in future studies.

Compliance with Ethical Standards

Conflict of Interest None.

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