



Review Article

# Coronavirus Disease (COVID-19) - Epidemiology, Detection and Management with Respect to the Indian Subcontinent - Current Updates and Theories

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## I N F O

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## A B S T R A C T

The outbreak of acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection in mid-December 2019, from Wuhan, Hubei Province, China, and its spread across China and beyond has taken the world by surprise. On March 11, 2020 WHO (World Health Organization) declared it a global pandemic. Herein, we discuss the epidemiological trends, clinical and diagnostic findings, management, and investigative therapies of this disease and also reflect upon how it might be different in India from the rest of the world.

**Keywords:** COVID-19, Coronavirus, Hydroxychloroquine, Peripheral Ground Glass Opacities, Remdesivir, RT-PCR

## Introduction

Coronaviruses are a group of diverse micro-organisms that primarily targets the human respiratory system. Previous outbreaks of coronaviruses (CoVs) include the Severe Acute Respiratory Syndrome (SARS)-CoV and the Middle East Respiratory Syndrome (MERS)-CoV which have been characterized as a great public health threat.<sup>1</sup> Coronavirus disease 19 (COVID-19) is an infection caused by a strain of coronavirus that was designated by the World Health Organization (WHO) as Severe Acute Respiratory Syndrome coronavirus 2 (SARS-CoV-2).

SARS-CoV-2 has a single-stranded positive-sense RNA genome and has been shown to interact with angiotensin-converting enzyme receptor-2 (ACE-2) for entry into the cells. The ACE-2 receptor is present in the alveolar cells of the lung, stomach, small intestine, colon, skin lymph nodes, brain, bile ducts, and parietal cells of the kidney.<sup>2</sup> Another recent study suggests that certain proteins of the virus like ORF8 (Open Reading Frame) and surface glycoprotein could bind to porphyrin and proteins like ORF1ab, ORF10 and ORF3a proteins attack the 1-beta chain of hemoglobin resulting in dissociation from iron to form porphyrin resulting in less



oxygen carrying capacity of hemoglobin.<sup>3</sup> Medications like hydroxychloroquine prevent the attack of ORF1ab, ORF10, and ORF3a proteins on heme, thus relieving symptoms of respiratory distress. The new antiretroviral drug Favipiravir inhibits the envelope protein and ORF7a protein, preventing the virus from entering the cells.<sup>3</sup>

WHO initially called the pathogen novel coronavirus 2019 (2019-nCoV) and the disease as Novel Coronavirus Infected Pneumonia (NCIP) only to rename the clinical condition as COVID-19 (short form of Corona Virus Disease-19). The Coronavirus Study Group (CSG) of the International Committee on Taxonomy of Viruses renamed the virus “Severe Acute Respiratory Syndrome Coronavirus 2” (SARS-CoV-2) on February 11, 2020.<sup>4,5</sup> On March 11, 2020 WHO declared COVID-19 a pandemic.

### Epidemiology

As of 27<sup>th</sup> of May, 2020, there are more than 5,609,079 cases worldwide and more than 350,958 deaths, in the USA there are 1,681,418 cases with more than 98,929 deaths and in India 151,767 cases with 4,337 deaths according to the tracker by The Lancet.<sup>6,7</sup> The phylogenetic analysis suggests that the disease appears to be zoonotic in origin, primarily bats.<sup>1</sup> The contagiousness is depicted by the basic reproduction number (R0) which is an indication of the transmissibility of a virus, representing the average number of new infections generated by an infectious person in a totally naive population. For  $R_0 > 1$ , the number infected is likely to increase, and for  $R_0 < 1$ , the transmission is likely to die out. The R0 for COVID-19 is between 2-3.<sup>8</sup> The median incubation period of COVID-19 disease is 5 days with 97.5% becoming symptomatic in 11.5 days and 100% symptomatic at 14 days.<sup>8</sup>

The Case Fatality Rate (CFR) or mortality rate for COVID-19 disease is about 3%.<sup>9</sup> Overall, the case fatality rate is 4.4%

worldwide. It may be depending on region and ethnicity; however, further research is warranted. Belgium has the highest CFR of 15.8%, followed by the United Kingdom 15%, France 14.9%, Italy 13.7%, Netherlands 12.4%, and Spain 11.7% among the top few. The United States has a CFR of 5.8%, China 4% and India 3.2%.<sup>10,11</sup> The recovery rate in India is 35.6%. The difference in the CFR may be caused by a number of factors like differences in the number of people tested (with more people tested identifies cases with milder illness and reduces the CFR), demographics (countries with older population has higher CFR) or health care system characteristics (more CFR with fewer resources). The Death Rate Doubling Time is used to access how long it takes for the total number of confirmed cases by COVID-19 to double. Longer the Doubling time better it is for the community. The Death Rate Doubling Time for India is 10 days, the USA is 18 days, the United Kingdom is 20 days, Italy is 32 days and for the world, it is 21 days. The Doubling Case Rate is used to access total confirmed cases of Coronavirus infection to double. Longer the Doubling Rate better the country is doing. The Doubling Case Rate in India is 11 days, in the United Kingdom it is 20 days, in the USA it is 21 days, in the world overall is 23 days and in Italy, it is 34 days.<sup>12</sup>

The disease primarily affects adults and rarely children. Human to human transmission is now the primary mode of transmission through droplets and fomites. Droplets nuclei travel up to 6 feet and do not linger in the air for long. The virus can be active in the air for about 3hrs, on copper 4hrs, on cardboard 24hrs, on steel and plastic for about 3 days. Risk factors for COVID-19 are age above 65years, people in long term care or nursing homes, immunocompromised patients, chronic lung disease, and co-morbid conditions like cardiac disease, diabetes, chronic renal disease, and chronic liver disease.<sup>13</sup>

### Clinical and Laboratory Features

### Definition of the Case and Contact by WHO<sup>14</sup>

**Table I. Definitions of case and contact by WHO<sup>14</sup>**

1.	Suspect Case	A patient with acute respiratory illness (fever and at-least one sign/symptom of respiratory disease like cough, dyspnea or diarrhea), AND history of travel to or residence in a country/area or territory reporting transmission of COVID-19 during 14 days prior to symptom onset. OR A patient with any acute respiratory illness AND contact with a confirmed or probable case of COVID-19 during 14 days prior to symptom onset. OR A patient with acute respiratory illness (fever and at-least one sign/symptom of respiratory disease like cough, dyspnea or diarrhea), AND requiring hospitalization AND no other etiology explaining the symptoms.
2.	Probable Case	A suspect case whose COVID-19 test result is inconclusive.
3	Confirmed Case	Laboratory confirmed COVID-19 case, irrespective of signs and symptoms.

4.	Contact	<p>A contact is a person that is involved in any of the following:</p> <ul style="list-style-type: none"> <li>• Providing direct care of COVID-19 patients without proper personal protective equipment (PPE).</li> <li>• Staying in the same close environment as a COVID-19 patient (including workplace, classroom, household, gatherings).</li> <li>• Travelling together in close proximity (within 1 meter) with a symptomatic person who later tested positive for COVID-19.</li> </ul>
5.	Low Risk Contact	<ul style="list-style-type: none"> <li>• Shared the same space (same classroom/same room for work or similar activity) and not having high risk exposure to the confirmed/suspected case.</li> <li>• Travel in the same environment (bus/train) but not having high exposure as cited above.</li> <li>• Any traveler from aboard not satisfying high risk criteria.</li> </ul>
6.	High Risk Contact	<ul style="list-style-type: none"> <li>• Contact with a confirmed case of COVID-19.</li> <li>• Travelers who visited a hospital where COVID-19 cases are being treated.</li> <li>• Travel to a province where COVID-19 local transmission is being reported as per WHO daily situation report.</li> <li>• Touched body fluids of patients (respiratory tract secretions, blood, vomitus, saliva, urine, feces).</li> <li>• Had direct physical contact with the body of the patient including physical examination without PPE.</li> <li>• Touched or cleaned the linens, clothes or dishes of the patient.</li> <li>• Close contact, within 3 feet (1 meter) of the confirmed case.</li> <li>• Co-passengers in an airplane/vehicle seated in the same row, 3 rows in front and behind of a confirmed COVID-19.</li> </ul>

Common clinical features associated with COVID-19 are fever (90%), dry cough (59%), fatigue (70%), anorexia (40%), and shortness of breath (31%). Other less common features associated are muscle or joint pains, sore throat, headache, chills, nausea or vomiting, loss of smell, and loss of taste and diarrhea.<sup>15</sup> The most distinctive symptom is shortness of breath which is not usually present in flu or the common cold. The clinical features are mostly similar to SARS-CoV and MERS-CoV.

The disease spectrum of SARS-CoV-2 ranges from mild disease (81%), severe (14%), and critical disease (5%) with the death rate of 3.4%. The severity of symptoms can be categorized as mild, moderate, severe, and critical (including ARDS, Sepsis, and shock). The patients with the mild or uncomplicated disease have mild symptoms of dry cough, some shortness of breath, sore throat, nasal congestion without radiographic abnormalities. The patients with moderate disease have fever, shortness of breath, cough, and other constitutional symptoms with radiographic abnormalities. The patients with severe disease have severe dyspnea with either a respiratory rate >30/min and/or SpO<sub>2</sub> <90% on room air and/or PaO<sub>2</sub>/FiO<sub>2</sub> <300 mmHg and more than 50% lung involvement on imaging within 24-48 hours. Critical patients have either respiratory failure, hypotension/septic shock, altered sensorium, or multi-organ failure. Severe complications include ARDS, acute cardiac injury, RNAemia, and multi-organ failure.<sup>16-18</sup>

Hospitalized patients develop arrhythmias in 17%, shock in 9%, bacterial superinfection in 10-20%, ARDS in 20%, respiratory co-infection in 2-25%, renal injury in 5%, and about 1/3<sup>rd</sup> develop cardiomyopathy. The recovery time is about 2 weeks for mild disease and 3-6 weeks for the severe disease.<sup>15</sup>

The laboratory features include lymphopenia, increased prothrombin time, elevated LDH (lactate dehydrogenase), elevated AST (aspartate aminotransferase), elevated ALT (alanine aminotransferase), elevated blood urea & creatinine, elevated ESR (erythrocyte sedimentation rate), increased CRP (C-reactive protein) and normal procalcitonin. In some cases, there may be an elevation of Anti pro-BNP and troponins. In severe cases, D-dimer is elevated increasing the possibility of pulmonary embolism even without deep venous thrombosis.<sup>19,20</sup>

### Prognostic Factors

Poor prognostic factors are age over 65 years (8% CFR in 70-79 years and 15% CFR in ≥80 years), male sex, co-morbidities {like diabetes, pulmonary disease, cardiovascular disease (including hypertension), malignancy, immunosuppression}, abnormal laboratory findings (severe lymphopenia, elevated troponin, elevated creatinine, elevated CRP, elevated creatinine, elevated LDH and elevated D-dimer).<sup>21</sup>

### Testing/ Screening Criteria

Indian Council of Medical Research (ICMR) suggested guidelines for the patients to be tested.<sup>22</sup> These include:

- All symptomatic patients (fever, cough, difficulty breathing) who have traveled internationally in the last 14 days.
- All symptomatic contacts of laboratory-confirmed cases.
- All symptomatic healthcare workers.
- All hospitalized patients with severe acute respiratory illness (fever and cough and/or shortness of breath).
- Asymptomatic contact of high-risk patients should be tested once between 5-14 days of contact.
- Direct and high-risk contact living in the same household and healthcare worker who examined the patient without adequate protection as per WHO.

## Diagnostics

The diagnostic tests include laboratory investigations and imaging.

### Laboratory Investigations

Essential samples to be taken are nasopharyngeal and oropharyngeal swabs; additionally, bronchoalveolar lavage, tracheal aspirate, and sputum can also be collected in select cases. The samples should be collected within 3 days of the onset of symptoms or as early as possible and no less than 7 days. Routine investigations like metabolic profile, culture for other respiratory pathogens must be sent for all patients.

Laboratory testing includes gene sequencing, Reverse Transcriptase Polymerase Chain Reaction (RT-PCR), and serological methods like Enzyme-Linked Immunosorbent Assay (ELISA). RT-PCR is a Nucleic Acid Amplification Test, widely used to detect viral RNA is based on spike-gene and N-gene with results available in 24hrs. RT-PCR targets e-gene (envelop gene, common to all coronaviruses) and RdRp gene (RNA-dependent RNA polymerase) & ORF-1 gene. The RdRp gene and ORF-1 gene are specific to SARS-CoV-2. RT-PCR has limitations of false positive and negative results and requires expensive equipment and trained personnel. RT-PCR with sputum induction was found to be better than in throat swabs and also decreases the risk to healthcare workers with aerosol generation. The sensitivity of RT-PCR is about 71%. In positive cases the virus has been isolated from blood, and rarely stool samples, raising the possibility of feco-oral transmission.<sup>23,24</sup> Viral gene sequencing should be regularly performed from a percentage of samples to monitor viral genome mutations.<sup>25</sup>

Reverse Transcription Loop-mediated Isothermal Amplification (RT-LAMP) allows faster and cheaper testing with results in less than 30 minutes. RT-LAMP is one-step nucleic acid amplification method based on PCR technology.<sup>26</sup> Rapid detection of nucleic acids can also be

achieved through the SHERLOCK platform (Specific High Sensitivity Enzymatic Reporter Unlocking) that uses cas13a ribonuclease for RNA sensing.<sup>27</sup>

Immunoglobulin G and Immunoglobulin M (IgG and IgM) can be detected from the serum of COVID-19 patients by ELISA. Point of care rapid tests based on immunochromatographic assay detects immunoglobulin G and immunoglobulin M (IgG and IgM) in patient's serum, plasma, or whole blood at the bedside.<sup>2</sup> IgG and IgM antibodies start developing in patients in about 5 days from the onset of symptoms.

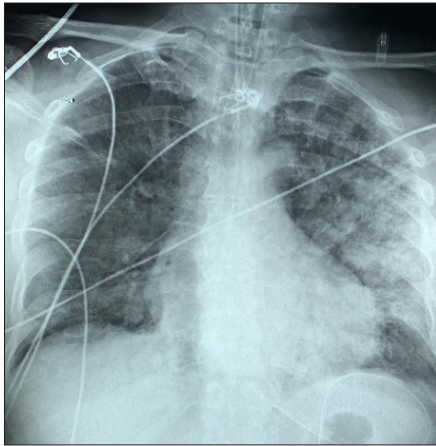
Recently developed new rapid point of care test, "ID NOWTM COVID-19" (Abbott) detects RNA-dependent RNA polymerase (RdRp). This test is 'emergency use authorized' by USFDA (United States Federation of Drug Authority), though not approved. It detects SARS-CoV-2 RNA in respiratory samples and gives a positive result in 5 minutes and a negative result in 13 minutes.<sup>28</sup>

Group testing is utilized as wide-scale individual testing is not feasible in a global pandemic. Many countries like Germany and now India are adopting group testing. This test detects the virus in a sample, be it from one person or a group (many individual samples). If the sample is negative, then the whole group is not a carrier of the virus. If the sample is positive, then at least one person in the group is a carrier. It is suggested that adequate use of group testing can save up to 85-95% of the tests.<sup>29</sup>

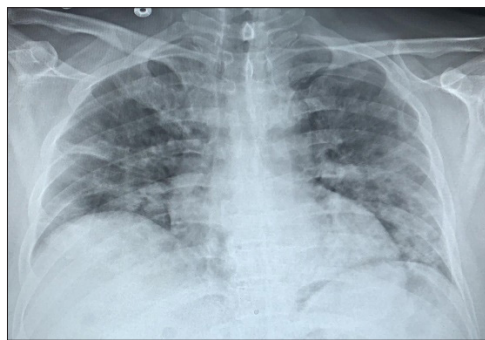
## Imaging

### Radiographic Findings

1. **Chest x-ray:** The chest x-ray may be normal in early or mild disease. The most common findings are bilateral air space opacities described as Ground-Glass Opacities (GGO) or consolidation, with peripheral and lower zone predominance (Figure 1 and 2). Pleural effusions are rare.<sup>30</sup> The extent of infection can be quantified by a severity score using the Radiographic Assessment of Lung Edema (RALE) score.<sup>31</sup> A score of 0-4 can be assigned to each lung depending on the extent of involvement by consolidation or GGO (0=no involvement; 1=<25%; 2=25-50%; 3=50-75%; 4=>75% involvement). The scores for each lung were summed to produce the final severity score.<sup>30</sup> More the score severe the disease.
2. **CT Scan:** CT chest has a lower rate of missed diagnosis of COVID-19 and should be used as a standard method for diagnosis of the disease. The sensitivity of CT chest for COVID-19 infection was found to be 98%, compared to RT-PCR sensitivity of 71%.<sup>24,32</sup> A non-contrast CT scan is advised in patients as contrast would affect the interpretation of ground-glass opacities. The CT findings also depend on the stage of the disease.<sup>33</sup>
3. Mild disease starts as small sub-pleural, unilateral or



**Figure 1.** Chest X-ray of 74-years-old male patient reveal bilateral airspace opacities with conglomeration in left mid and lower zones suggesting consolidation. The endotracheal tube is in place. Multiple overlying ECG leads. Radiographic score 4+4=8. The patient was RT-PCR positive for COVID-19



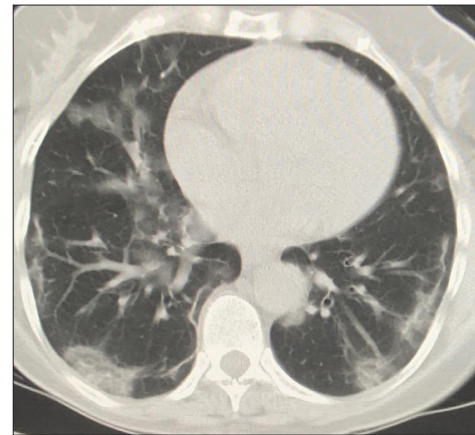
**Figure 2.** Chest X-ray of 53-year-old female patient reveal low lung volumes with bilateral mid and lower zone airspace opacities with conglomeration in left mid and lower zones and right lower zone suggesting consolidation. Radiographic score 2+3=5. The patient was RT-PCR positive for COVID-19

bilateral GGO in lower lobes which later develops into a crazy-paving pattern and eventually consolidation.

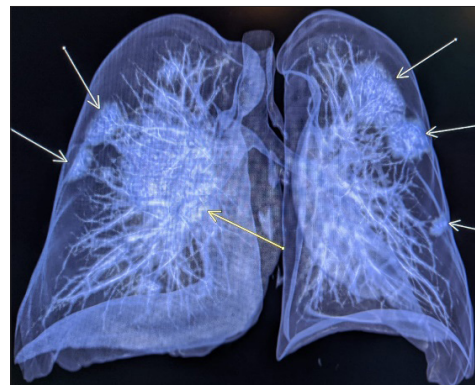
4. In early stages (0-4 days after onset of initial symptoms) unilateral or bilateral lower lobe GGO is the main presentation.
5. In progressive stage (5-8 days after initial symptoms) there are bilateral, multi-lobar GGO with crazy paving pattern and consolidation.
6. In peak stage (9-13 days after initial symptoms) there is diffuse bilateral GGO with crazy paving pattern and consolidation.
7. In the absorption stage (more than 14 days after initial symptoms) there is a gradual resolution of consolidation and GGO. No crazy paving pattern is observed.

Peak lung involvement is characterized by crazy paving pattern, new or increasing consolidation, bilateral, and

multi-lobar involvement (Figure 5). Pleural effusions, extensive tiny nodules, and lymphadenopathy are rare (Figure 3 and 4).<sup>34, 35</sup> Microvascular dilatations in the area of GGO has been observed on CT scan, probably secondary to inflammation.<sup>36</sup>



**Figure 3.** Non-contrast CT scan of the Chest of the 62-year-old female patient reveals peripheral, bilateral (multi-lobar), lower lobes GGO of rounded morphology. The patient was RT-PCR positive for COVID-19



**Figure 4.** 3D CT Chest of another COVID-19 positive patient showing rounded peripheral, bilateral GGOs



**Figure 5.** Non-contrast CT scan of the Chest of the 72-years-old male patient reveals peripheral, bilateral (multi-lobar), GGO with crazy-paving pattern. The patient was RT-PCR positive for COVID-19

According to the consensus statement by Radiological Society of North America (RSNA) the typical findings are peripheral, bilateral (multi-lobar), GGO, or multifocal GGO of rounded morphology with or without consolidation or visible interlobular lines (crazy-paving pattern) and reverse halo sign. The intermediate findings of COVID-19 are multifocal, diffuse, perihilar, or unilateral consolidation or GGO without specific distribution and are non-peripheral or non-rounded. The atypical findings of COVID-19 are isolated lobar or segmental consolidation without GGO, centrilobular or tree-in-bud nodules, cavitation, smooth interlobular septal thickening with pleural effusion.<sup>37</sup>

Although the imaging features of COVID-19 closely resemble with SARS-CoV (Severe Acute Respiratory Syndrome) and MERS-CoV (the Middle East Respiratory Syndrome coronavirus), the bilateral lung involvement and absence of nodules is more suggestive of COVID-19, as initial findings in SARS-CoV and MERS-CoV are more commonly unilateral.<sup>38,39</sup> Non-COVID-19 cases of pneumonia, on CT, has central and peripheral distribution, lobar or segmental distribution, pleural thickening, pleural effusion, and lymphadenopathy.<sup>40</sup>

## Disease Prevention

**Preventing exposure in the community:** The aim of preventions is to break the transmission of the virus. This can be achieved through physical and social distancing, by staying at home and maintaining at least 6 feet (2 meters) distance from others. Repeated handwashing with soap and water for at least 20 seconds, with hand sanitizer containing at least 60% ethyl alcohol or isopropyl alcohol and avoiding touching eyes, nose, and mouth with unwashed hands is recommended.<sup>41</sup> Covering mouth and nose with a cloth or mask when going out in public and covering a cough and sneeze with a cloth covering the face or sneeze inside the elbow.<sup>42</sup> Standard, contact, airborne, and droplet precautions to be followed. The standard precautions include hand hygiene, use of personal protective equipment, respiratory hygiene and cough etiquette, cleaning and disinfection of surfaces and environment, appropriate patient placement, and waste disposal. Environmental disinfection can be performed with a number of agents the most common ones are bacillol spray (ethanol and propranolol), 7% Lysol spray (80% benzalkonium chloride solution, laurel alcohol ethoxalate) and Avaguard™ hand rub (2-propranolol, 1-propranolol), hypochlorite solution and detergent soap.<sup>41</sup>

**Preventing exposure in the healthcare setting:** Screening for all patients suspected for COVID-19. The healthcare personnel are advised to wear Personal Protective Equipment (PPE) covering their exposed body parts and following standard, contact, and droplet precautions with the gown, gloves, mask, and eye protection. Airborne precautions like respirators (N95) are warranted for

aerosol-generating procedures (intubation, bronchoscopy, nebulization, etc.). Due to a worldwide shortage of PPE, decontamination for reuse has been advised with hydrogen peroxide, Ultraviolet light, and moist heat. Environmental disinfection can be achieved by 1% sodium hypochlorite solution. For the disinfection of items like thermometers, stethoscopes, BP apparatus cuffs, 60% ethyl alcohol can be used. Quaternary ammonium compounds are highly virucidal.<sup>43-45</sup>

## Treatment

The treatment depends on the severity of the disease. There is no approved specific antiviral drug for COVID-19. Many investigative therapies are under trial; however, these are used clinically due to lack of specific medication for COVID-19. We discuss a few commonly used medications under trial before specific treatment strategies:

- **Hydroxychloroquine/Chloroquine and Azithromycin:** Some initial reports have reported that 600 mg of hydroxychloroquine daily significantly reduced the viral load in nasopharyngeal swab and addition of Azithromycin increased efficiency of virus elimination. The common side effects of Hydroxychloroquine/Chloroquine include QT prolongation, cardiomyopathy, hepatotoxicity, bone marrow suppression.<sup>46</sup> Both Hydroxychloroquine/Chloroquine and Azithromycin cause QT prolongation, hence EKG monitoring is required. However, further clinical trials are warranted.
- **Lopinavir/ Ritonavir:** Some initial reports have shown in vitro activity of Lopinavir/Ritonavir against SARS-CoV-1 and MERS-CoV; however, no significant difference than standard care has been observed in SARS-CoV-2. With a lack of medication experts suggest keeping this combination as a treatment option.<sup>47</sup>
- **Remdesivir:** In vitro studies have shown that Remdesivir (neuraminidase inhibitor, inhibits viral replication) is highly effective in controlling SARS-CoV-2. Preliminary studies have shown Remdesivir shortens the recovery time in adults with COVID-19 and lower respiratory infections.<sup>48</sup>
- **Dexamethasone:** Dexamethasone, a corticosteroid is known to reduce inflammation. Initial insights in patients in United Kingdom has shown to reduce mortality in patients requiring oxygen or ventilator support. WHO has welcomed further trials and research.<sup>49</sup>
- **Vitamin C:** Vitamin C is an antioxidant and prevents inflammatory damage to alveolar cells.
- **Favipiravir:** Favipiravir is an RNA dependent RNA polymerase inhibitor and is recently approved to treat COVID-19. It has been used to treat infection by RNA viruses. Clinical trials are underway.<sup>50</sup>
- **Arbidol:** Some studies have shown that Arbidol, an

antiviral drug inhibits SARS-CoV-2 infection in vitro.<sup>51</sup>

- **Tocilizumab:** Tocilizumab is an IL-6 antagonist. Inhibition of IL-6 results in a reduction in cytokine and acute phase reactant production. Studies have shown that symptoms, blood gases, and CT opacities improved after treatment with Tocilizumab.<sup>51</sup>
- **Interferon Beta:** Interferon beta has been used to reduce viral overload in MERS-CoV, however, studies are underway for its role in treating SARS-CoV-2.<sup>52</sup>
- **Interferon Alfa:** Interferon alfa is a broad-spectrum antiviral and has been shown to inhibit SARS-CoV reproduction in vitro.<sup>50</sup>
- **Convalescent Serum:** Patients who have recovered from COVID-19 infection have antibodies in their serum. Studies have shown clinical improvement after the administration of convalescent serum containing neutralizing antibodies to COVID-19 patients with ARDS.<sup>53</sup> In India, clinical trials with convalescent serum have started.
- **Ribavirin:** Ribavirin is a nucleoside analog and with broad-spectrum antiviral effects. Ribavirin combined with Lopinavir/ Ritonavir reduces the risk of ARDS.<sup>50</sup>
- **Ivermectin:** Ivermectin is a broad-spectrum antiparasitic drug and has been shown to inhibit SARS-CoV-2 reproduction in vitro.<sup>54</sup>
- **Ribonucleoside analog  $\beta$ -d-N4-hydroxycytidine:** Recent study by Sheahan et al. has shown that ribonucleoside analog  $\beta$ -d-N4-hydroxycytidine has broad-spectrum antiviral activity against SARS-CoV-2, MERS-CoV, SARS-CoV, and related zoonotic group 2b or 2c bat-CoVs, and increased potency against a CoV bearing resistance mutations to the nucleoside analog inhibitor Remdesivir.<sup>55</sup>
- **Vaccine:** Many countries are working hard to prepare a vaccine but, none is available in the market so far. The vaccine technologies under evaluation are whole virus vaccines, recombinant protein subunit vaccines, and nucleic acid vaccines.<sup>56</sup> There are 115 candidates for the COVID-19 vaccine worldwide, of which 78 are confirmed as active and 37 are unconfirmed. Of the 78 confirmed active projects, 73 are currently at exploratory or preclinical stages, with some in clinical stages, including mRNA-1273, Ad5-nCoV, INO-4800, LV-SMENP-DC, and pathogen-specific aAPC.<sup>57</sup> Among those with the greatest potential for speed is DNA- and RNA-based platforms, as these can be made quickly because they require no culture or fermentation, instead of using synthetic processes, followed by those for developing recombinant-subunit vaccines.<sup>58</sup>

### Prophylaxis

Though there are ongoing clinical trials ICMR recommended Hydroxychloroquine for healthcare workers directly involved in patient care of suspect or confirmed COVID-19 patient

(400 mg twice daily day 1, then 400 mg once weekly for 7 weeks) and asymptomatic close contacts of confirmed COVID-19 patient (400 mg twice daily day 1, then 400 mg once weekly for 3 weeks). Before administration G6PD test and ECG should be performed.<sup>59,60</sup>

### Hospital Admission Criteria

The criteria for hospital admission are respiratory rate more than 24/min, SpO<sub>2</sub> <94% at room air, confusion, drowsiness, systolic BP <90mmHg or diastolic BP <60 mmHg and high-risk patients (age above 60 years, comorbidities as described earlier). MuLBSTA scoring system proposed by Chen et.al. includes six indices: Multilobar infiltrates (5 points), Lymphopenia (4 points), Bacterial Co-infection (4 points), Smoking history (Active smoker 3 points, quit smoking 2 points), Hypertension (2 points), Age >60 years (2 points). If the score is more than 12 there is increased mortality.<sup>18</sup>

### Mild Cases

Mild cases present with mild fever, cough and prostration, without clinical or laboratory parameters of clinical severity or respiratory impairment. The treatment is mainly symptomatic with antipyretic (paracetamol), antibiotics if needed (azithromycin with or without amoxicillin and clavulanate), hydration, oseltamivir if influenza is also suspected. Home isolation should continue till 2 negative PCR tests 24hrs apart and till 2 weeks after the symptoms resolve.<sup>61</sup>

### Supportive Management

In patients with severe acute respiratory illness, respiratory distress, hypoxemia, and shock early supportive management with 5L/min supplemental oxygen therapy increasing to 10-15 L/min to keep target SpO<sub>2</sub> >90% is recommended. Conservative fluid therapy to keep lungs dry but avoid hypovolemia, empiric antibiotics according to clinical diagnosis (community-acquired pneumonia or healthcare-associated pneumonia or sepsis), neuraminidase inhibitor (oseltamivir), and treatment of comorbidities. Empiric corticosteroids are not recommended for the treatment of viral pneumonia or ARDS. Severe complicated COVID-19 patients often require intubation. There is microvascular thrombosis, according to autopsy series from Italy, which leads to increased dead space. Hypoxemic respiratory failure and ARDS are managed with high flow nasal catheter or non-invasive ventilation. Endotracheal intubation should be performed in severe or critical cases.<sup>16</sup> In mechanical ventilation, low tidal volumes and low inspiratory pressures are recommended.<sup>62</sup> Prone ventilation for >12hrs/day is also recommended.<sup>63</sup> Further discussion on mechanical ventilation is beyond the scope of this manuscript.

### Moderate Cases

Moderate cases present with signs and symptoms

of COVID-19 like high fever, persistent cough, severe asthenia, prostration, with clinical or radiological signs of lung involvement and without red flags of clinical severity or respiratory impairment. These patients are closely monitored and may require hospital admission. Perform chest x-ray (first-line investigation) or CT Chest without IV contrast (high sensitivity in identifying and quantifying the parenchymal involvement) as indicated. The treatment includes supportive management, oral hydration, consider broad-spectrum empiric antibiotic therapy. Antiviral therapy with Lopinavir/Ritonavir 200/50mg tablets, 2 tablets twice daily for 14 days and hydroxychloroquine 400 mg twice daily day 1, then 200 mg twice daily for 10 days or chloroquine phosphate 250 mg twice daily for 10 days. An alternative to Lopinavir/Ritonavir, Darunavir 600 mg tablet, 1 tablet twice daily plus Ritonavir 100 mg tablet, 1 tablet twice daily for 14 days.<sup>61</sup>

### Severe Cases

Patients with clinical and/or laboratory parameters of worsening gas exchange (dyspnea, elevated respiratory rate, decreased SpO<sub>2</sub>, altered blood gas on room air) without critical or warning signs like respiratory failure, altered consciousness, hypotension, or shock. Perform SARS-CoV-2 RT-PCR swab every 48-72hrs until persistently negative, IL-6 (Interleukin-6) levels, D-dimer, and inflammatory markers like fibrinogen, ferritin, CRP and LDH, chest x-ray, CT chest, and echocardiography to assess the lungs and heart. The treatment includes supportive management, oral hydration, and consider broad-spectrum empiric antibiotic therapy. Antiviral therapy with Remdesivir once-daily IV, 200mg on day 1 then 100 mg once daily for 10 days or Lopinavir/Ritonavir 200/50 mg tablets, 2 tablets twice daily for 28 days and hydroxychloroquine 400 mg twice daily day 1, then 200mg twice daily for 10 days or chloroquine phosphate 250 mg twice daily for 10 days and Tocilizumab 8 mg/kg single dose IV infusion in 60 minutes or two doses if no clinical improvement. ICMR recommends off-label use of hydroxychloroquine 400 mg loading dose followed by 200 mg twice daily for 4 days in combination with azithromycin 500mg once daily for 5 days, along with close monitoring of the EKG for QTc interval prolongation.<sup>16</sup> An alternative to Lopinavir/Ritonavir, Darunavir 600 mg tablet, 1 tablet twice daily plus Ritonavir 100 mg tablet, 1 tablet twice daily for 14 days. Tocilizumab should be considered if any one or more of the following is present like PaO<sub>2</sub>/FiO<sub>2</sub> <300 mmHg, rapid worsening of blood gas, IL-6 levels >40 pg/mL or D-dimer >1000 ng/mL. Steroids (methylprednisolone or dexamethasone) may be considered if there is an incipient worsening of respiratory functions and if Tocilizumab is administered.<sup>61</sup>

### Critical Cases

These patients have very severe illnesses due to respiratory

failure, ARDS, hypotension, multi-organ failure, or impaired consciousness. Perform SARS-CoV-2 RT-PCR swab every 48-72hr until persistently negative, IL-6 levels, D-dimer, and inflammatory markers like fibrinogen, ferritin, CRP, and LDH, CT chest and echocardiography to assess the lungs and heart. The treatment includes antiviral therapy, supportive management, oral hydration and consider broad-spectrum empiric antibiotic therapy. Supportive therapy with early mechanical ventilation, and ECMO (Extra Corporal Membrane Oxygenation) in case of refractory hypoxemia. Antiviral therapy with Remdesivir or Lopinavir/Ritonavir and hydroxychloroquine or chloroquine phosphate and Tocilizumab or Darunavir with Ritonavir or Tocilizumab and steroids may be administered as mentioned in the treatment of severe cases. Dexamethasone has been introduced for cases requiring oxygen or ventilator support.<sup>49</sup>

### Hospital Discharge Criteria for a Suspect or Confirmed COVID-19 Case

The samples from a suspect or probable case of COVID-19 are sent to the laboratory and the patient is kept in isolation until the test results. If the result is negative, then the patient is discharged according to the physician's discretion with monitoring for 14 days since the last contact with confirmed COVID-19 case. In case the results of the test are positive, then the case is managed as per the management guidelines and shall be discharged after clinical and radiological improvement with viral clearance in respiratory samples in two negative RT-PCR 24-48hrs apart after 2 weeks of treatment.<sup>64</sup>

### Special Considerations for India

There have been many theories regarding the severity of COVID-19 in various parts of the world. We discuss some theories attributable to the Indian subcontinent.

- Sequencing of COVID-19 genome: Gene sequencing analysis of the SARS-CoV-2 genome from different locations like USA, Italy, India, and Nepal was performed and revealed that the maximum number of mutations were found in Indian sequence. Mutation in the viral genome which is supposed to bind to human miRNA-27b has led to the efficacy of antiretroviral drugs in COVID-19 in India, whereas in China these drugs were ineffective. It is speculated that due to these factors there is varied disease severity in different countries.<sup>65</sup>
- Universal Bacillus Calmette-Guerin (BCG) Vaccine: Studies have found that BCG vaccination has been found to provide protection against respiratory pathogens. There has been more morbidity and mortality in countries like Italy, the USA, Netherland without universal BCG vaccination. COVID-19 attributable mortality has been 5.8 times lower in countries among BCG using countries than in non-BCG using countries.



Compulsory BCG vaccination has a negative correlation with COVID-19 mortality and morbidity.<sup>66-68</sup>

- Population density: Though it is expected that the population density would result in the spread of the disease, but research has shown that the mortality rates do not correlate with population density.<sup>68</sup>
- Ventilated homes: Many studies have shown that well-ventilated homes with high levels of natural sunlight, natural ventilation, and cleanliness can protect against indoor droplet infection.<sup>69,70</sup> India like many developing countries has well-ventilated homes with plenty of natural sunlight. Thus, it is postulated that COVID-19 will be less virulent as compared to many developed countries like the USA or Italy.
- Blood group A: Studies have shown that COVID-19 is more prevalent in people with blood group A. In India, the prevalence of blood group A is between 23-30%, whereas countries like the USA and Britain have 41% and 42% respectively. This correlation may suggest that COVID-19 will be less widespread in India.<sup>71</sup> But this is just an observation and further investigation is required to prove this.
- Younger population: Mortality of elderly patients with COVID-19 is higher than younger and middle-aged patients. India has about 9% population above the age of 60 and the majority is the young population.<sup>72,73</sup>

## Conclusion

Substantial work has to be done to combat the COVID-19 pandemic at the individual, institutional, and administrative levels. Many pharmacologic strategies are under investigation with many clinical trials underway. Effective prevention through social and physical distancing, public health education, and vigilant infection control is recommended. There is still a long way before a vaccine becomes available, till that time the best strategy is prevention.

**Conflicts of Interest:** None

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