

## COVID-19 : A Review

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### ABSTRACT

In the beginning of year 2020, a novel corona virus possibly originated from the bats and caused an outbreak in the city of Wuhan in China. By the end of January SARS-CoV-2 had demonstrated sustained human to human transmission with dangerously high R<sup>0</sup>. By 30th of January World Health Organization declared SARS-CoV-2 outbreak as Public Health Emergency of International Concern (PHEIC).<sup>1</sup> This pandemic showed, that the world was again not prepared for pandemic due to the virus. Soon Thailand became the first country affected outside China. Italy, Spain and UK became the hotspots of virus in the Europe. The study led by virologist Neeltje van Doremalen and colleagues showed that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed)<sup>3</sup>. Male sex with higher age and other co-morbidities like Obesity, Hypertension, uncontrolled DM, ischemic heart disease, chronic liver disease and chronic kidney disease are important risk factors. The incubation period of COVID-19 on an average is 5 to 11 days. Clinical manifestations of 2019-nCoV infection include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia. Less common symptoms include headache, dizziness, abdominal pain, diarrhoea, nausea, and vomiting. Very few COVID-19 patients show prominent upper respiratory tract symptoms and signs, suggesting that virus has greater predilection for lower respiratory tract involvement. Pregnant and non-pregnant women have similar characteristics<sup>11</sup>. CDC recommends nasopharyngeal and oropharyngeal swab by RT PCR for diagnosis. A high level of IL 6, d Dimer & CRP indicates progressive disease and poor prognosis. CT shows bilateral multilobar ground-glass opacification (GGO) with a peripheral distribution, mainly in the lower lobes. Favipiravir and Remdesivir are potential definite therapies in mild to moderate disease along with Tocilizumab and convalescent plasma in sicker patients. We hope to use these therapies judiciously at a right point of time in the course of illness for optimal outcomes.

### Background :

In the beginning of year 2020, a novel corona virus possibly originated from the bats and caused an outbreak in the city of Wuhan in China. Initially it was thought that SARS-CoV-2 is a zoonosis and hence unlikely to have human to human transmission.

However few Chinese doctors and public health officials could note that most of the people in the families were developing this pneumonia and Chinese Healthcare system was soon overwhelmed with the patients.

By the end of January SARS-CoV-2 had demonstrated sustained human to human

transmission with dangerously high R<sup>0</sup>. By 30th of January World Health Organization declared SARS-CoV-2 outbreak as Public Health Emergency of International Concern (PHEIC).<sup>1</sup>

This pandemic showed, that the world was again not prepared for pandemic due to the virus. Soon Thailand became the first country affected outside China. There was a sudden surge of cases in some countries like Italy and Iran. Italy, Spain and UK became the hotspots of virus in the Europe. The virus then rapidly spread to remaining countries of the world infecting 92,77,392 people and killing 4,76,825 people with a global mortality rate of around 3.4 %<sup>2</sup>

### Transmission :

Initially as countries struggled to contain the virus, medical professional and public health personnel all over the world continued to remain perplexed about the route of transmission. Person-to-person transmission was thought to occur among close

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contacts mainly via respiratory droplets produced when an infected person coughs or sneezes. Fomites may be an important source of transmission, as SARS-CoV has been found to persist on surfaces up to 96 h and other corona viruses for up to 9 days. The study led by virologist Neeltje van Doremalen and colleagues showed that aerosol and fomite transmission of SARS-CoV-2 is plausible, since the virus can remain viable and infectious in aerosols for hours and on surfaces up to days (depending on the inoculum shed)<sup>3</sup>.

Later on Two papers published in Euro surveillance and New England journal of Medicine, first one describing transmission in cruise ship Diamond Princess<sup>4</sup> and later paper describing transmission in one of the nursing care facility in Washington<sup>5</sup> gave important insights about dynamics of transmission

Two facts emerged from these papers

1. That this virus has sustained airborne transmission.
2. There are significant transmission happening through asymptomatic or presymptomatic people.

These 2 papers changed the direction of control efforts of this virus.

As more evidence emerged, it became clear that most pre-symptomatic patients have very high viral loads and they spread the virus in their close contacts before they actually become ill. Asymptomatic people who never develop symptoms) have less viral load and only few of them who are older in age having comparatively higher viral loads are capable of infecting others.<sup>6</sup>

This brought major change in the public health containment efforts. Different types of mask became the defence against the virus. The countries which were traditionally using mask as a part of their culture saw slower trajectory of the pandemic

Secondary attack rate in SARS CoV-2 infections was 11.2 to 13.8% in some Chinese studies.<sup>7</sup> Exact rate of nosocomial transmission of COVID-19 is not yet known. Healthcare workers can be infected through exposure in the hospital or exposure

through the community. Prolonged exposure without adequate PPE and exposure to aerosol generating procedures is found to be most important risk factor for infection. (MMWR)<sup>8</sup>

#### **Risk factors :**

The most important risk factor is age<sup>9</sup>. Male sex with higher age and other comorbidities are considered serious risk factors. Obesity, Hypertension, uncontrolled DM, ischemic heart disease, chronic liver disease and chronic kidney disease are important risk factors observed in Indian Population.

#### **Clinical features :**

The incubation period of COVID-19 on an average is 5 to 11 days. Commonest clinical feature is dry cough and fever. Most of the patients start developing severe pneumonias in the end of first week of illness.

Clinical manifestations of 2019-nCoV infection include fever, dry cough, dyspnoea, chest pain, fatigue and myalgia. Less common symptoms include headache, dizziness, abdominal pain, diarrhoea, nausea, and vomiting.<sup>10</sup> Difference from SARS-CoV and MERS-CoV infections, however, is that very few COVID-19 patients show prominent upper respiratory tract signs and symptoms such as rhinorrhoea, sneezing, or sore throat, suggesting that the virus might have greater preference for infecting the lower respiratory tract. Pregnant and non-pregnant women have similar characteristics<sup>11</sup>. Severe complications such as hypoxemia, acute ARDS, arrhythmia, shock, acute cardiac injury, and acute kidney injury have been reported among COVID-19 patients. A study among 99 patients found that approximately 17% patients developed ARDS and, among them, 11% died of multiple organ failure<sup>12</sup>. The median duration from first symptoms to ARDS was 8 days.<sup>13</sup>

Clinical syndromes classified as per MOHFW clinical management guidelines

1. Uncomplicated illness
2. Mild pneumonia
3. Severe pneumonia

4. ARDS
5. Sepsis
6. Septic shock

#### **Diagnosis :**

Ministry of health and family welfare has described case definitions on its websites. Probable cases are those for whom testing for SARS-CoV-2 is inconclusive or whose test could not be done in spite of clinical suspicion. A confirmed case is one with a laboratory confirmation of SARS-CoV-2 infection, irrespective of clinical signs and symptoms.<sup>14</sup> For patients who meet diagnostic criteria for SARS-CoV-2 testing, the CDC recommends collection of specimens from the upper respiratory tract (nasopharyngeal and oropharyngeal swab) and, if possible, the lower respiratory tract (sputum, tracheal aspirate, or bronchoalveolar lavage). The testing can be done by open RT PCR or closed RT PCR (Liketrunat or genxpert)

#### **Laboratory findings :**

Among COVID-19 patients, common laboratory abnormalities include lymphopenia, prolonged prothrombin time, and elevated lactate dehydrogenase. ICU-admitted patients had more laboratory abnormalities compared with non-ICU patients. Some patients had elevated aspartate aminotransferase, creatine kinase, creatinine, and C-reactive protein. Most patients have shown normal serum procalcitonin levels<sup>13</sup>. A progressively high level of IL 6, d dimer and CRP indicates progression of disease and poor prognosis.

#### **Radiology findings :**

Known features of COVID-19 on initial CT include bilateral multilobar ground-glass opacification (GGO) with a peripheral or posterior distribution, mainly in the lower lobes and less frequently within the right middle lobe. Atypical initial imaging presentation of consolidative opacities superimposed on GGO may be found in a smaller number of cases, mainly in the elderly population. Septal thickening, bronchiectasis, pleural thickening, and subpleural involvement are some of the less common findings, mainly in the later stages

of the disease. Pleural effusion, pericardial effusion, lymphadenopathy, cavitation, CT halo sign, and pneumothorax are uncommon but may be seen with disease progression. Follow-up CT in the intermediate stage of disease shows an increase in the number and size of GGOs and progressive transformation of GGO into multifocal consolidative opacities, septal thickening, and development of a crazy paving pattern, with the greatest severity of CT findings visible around day 10 after the symptom onset<sup>15</sup>

#### **Treatments :**

The science is constantly evolving on the treatment of covid-19. Isolation and supportive care including oxygen therapy, fluid management, and antibiotics treatment for secondary bacterial infections is recommended. Some COVID-19 patients progressed rapidly to ARDS and septic shock, which was eventually followed by multiple organ failure. Therefore, the effort on initial management of COVID-19 must be addressed to the early recognition of the suspect and contain the disease spread by immediate isolation and infection control measures.

There are many experimental therapies emerging in last couple of months in different parts of the world. The data is abundant however real quality data and randomized controlled trials which can really guide the clinicians are still scant

#### **Role of HCQS :**

HCQs was first such therapy, data of which was initially published by French researchers which showed better viral clearance in the patients with HCQS arm.<sup>16</sup>

Two open-label randomized trials in 150<sup>17</sup> and 30 patients<sup>18</sup> in China reported no difference in clearance of SARS-CoV-2 RNA, nor clinical outcome, in patients with mild-moderate disease with HCQ vs. no HCQ. The former had higher total (21 vs. 7) and serious (2 vs. 0) adverse events, but was stopped early.

Another Chinese randomized trial<sup>19</sup> of 62 hospitalized patients reported quicker 'time to clinical recovery' (by 1 day) & more common

radiological improvement if treated with HCQ vs. not (no placebo), with no severe adverse effects.

Analysis of multinational surgical outcomes registry data on ~96,000 patients hospitalized with COVID-19 suggested **increased risk of mortality and ventricular arrhythmia** in those receiving CQ or HCQ +/- a macrolide (clarithromycin / azithromycin)<sup>20</sup>. This study was later retracted due to widespread criticism. The world is still awaiting conclusive data on therapeutic role of HCQs in the treatment of covid illness.

#### **Role of Steroids :**

After initial guidelines about negative remarks about use of steroid in severe disease, Recovery Trial conducted by oxford university stopped recruiting patients in dexamethasone arm which demonstrated that dexamethasone 6 mg once per day (either by mouth or by intravenous injection) for ten days reduced deaths by one-third in ventilated patients (rate ratio 0.65 [95% confidence interval 0.48 to 0.88]; p=0.0003) and by one fifth in other patients receiving oxygen only (0.80 [0.67 to 0.96]; p=0.0021). There was no benefit among those patients who did not require respiratory support (1.22 [0.86 to 1.75]; p=0.14).<sup>21</sup>

In an another single center retrospective Spanish cohort, In hospital mortality was reduced by 41.8% in steroid treatment compared to no steroid treatment.<sup>22</sup>

#### **Role of Convalescent plasma :**

In the first RCT that included 103 patients and was terminated early, the hazard ratio for time to clinical improvement within 28 days in the convalescent plasma group was 1.40 and was not statistically significant.<sup>23</sup>

#### **Role of Tocilizumab :**

Severe COVID-19 can manifest in rapid decompensation and respiratory failure with elevated inflammatory markers. This presentation is consistent with cytokine release syndrome in chimeric antigen receptor T cell therapy, for which IL-6 blockade is approved treatment. In one study assessed effectiveness and safety of IL-6 blockade

with tocilizumab in a single-center cohort of patients with COVID-19 requiring mechanical ventilation. Tocilizumab was associated with a decreased likelihood of death despite higher superinfection occurrence.<sup>24</sup> Randomized controlled trials are urgently needed to confirm these findings.

#### **Role of Remdesvir :**

REMDESIVIR in a published RCT shortened duration of illness in moderately ill patients needing oxygen but not ventilated from 15 to 11 days. It also reduces mortality from 11.9 to 7%. Just short of statistical significance<sup>25</sup>

#### **Role of Favipiravir :**

One non-randomized before-vs-after comparison study of favipiravir vs. lopinavir / ritonavir (both groups also received adjunctive interferon) in 80 patients hospitalized in China reported possible quicker loss of SARS-CoV-2 RNA in upper respiratory specimens and improvement in CT scan with favipiravir, with several methodological and reporting flaws<sup>26</sup>

One preprint of a RCT comparing favipiravir with Arbidol (umifenovir) in 240 patients with mostly moderate disease (<50% had confirmed COVID-19 by PCR). Primary outcome of clinical recovery at 7 days was similar between groups (61% vs 52%, p=0.13).<sup>27</sup>

A preprint open label RCT of favipiravir vs. baloxavir vs. neither (1:1:1 ratio; 30 participants) reported similar negative PCR at 7 days (control 10/10; 7/10 balox.; 7/9 favi.) and time to clinical improvement (14-15 days). Two in the favipiravir group went to ICU.<sup>28</sup>

#### **Conclusions :**

The current COVID-19 pandemic is clearly an international public health problem. There have been rapid advances in what we know about the pathogen, how it infects cells and causes disease, and clinical characteristics of disease. As we are getting more information about the disease transmission, our principles of infection control are getting finer. There is also more and more data about investigational therapies. Favipiravir and



Remdesivir are appearing potential definite therapies in mild to moderated disease however several centers are using Tocilizumab and convalescent plasma in sicker patients successfully. Till more and more evidence emerge, we hope to use all these therapies judiciously at a right point of time in the course of illness without causing an excessive harm to the patients.

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