Coronavirus Disease: A Review of A New Threat To Public Health

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Abstract- *There is a new public health crises threatening the world with the emergence and spread of 2019 novel coronavirus (2019-nCoV) or the severe acute respiratory syndrome coronavirus 2 (SARSCoV-2). The virus originated in bats and was transmitted to humans through yet unknown intermediary animals in Wuhan, Hubei province, China in December 2019. The disease is transmitted by inhalation or contact with infected droplets and the incubation period ranges from 2 to 14 d. The symptoms are usually fever, cough, sore throat, breathlessness, fatigue, malaise among others. The disease is mild in most people; in some (usually the elderly and those with comorbidities), it may progress to pneumonia, acute respiratory distress syndrome (ARDS) and multi organ dysfunction. Many people are asymptomatic. The case fatality rate is estimated to range from 2 to 3%. Diagnosis is by demonstration of the virus in respiratory secretions by special molecular tests. Common laboratory findings include normal/ low white cell counts with elevated C-reactive protein (CRP). The computerized tomographic chest scan is usually abnormal even in those with no symptoms or mild disease. Treatment is essentially supportive; role of antiviral agents is yet to be established. Prevention entails home isolation of suspected cases and those with mild illnesses and strict infection control measures at hospitals that include contact and droplet precautions. The virus spreads faster than its two ancestors the SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), but has lower fatality. The global impact of this new epidemic is yet uncertain.*

Keywords- 2019-nCOV, SARS-CoV-2, COVID-19, Pneumonia, Review

I. INTRODUCTION

Over the last few decades, the world has seen the existence of new viruses that posed serious threats to global health. In late December 2019, several patients in Wuhan, China started reporting symptoms that resembled pneumonia. A new virus was identified and initially called the 2019 novel coronavirus (2019-nCoV). The World Health Organization (WHO) eventually changed the name of the virus to severe acute respiratory syndrome coronavirus 2 (SARS-CoV2) [1]. The disease it causes has been named coronavirus disease 2019 (COVID-19). The SARSCoV is a positive-stranded RNA virus that originates from the Coronaviridae family. Other viruses from the same family include the severe acute respiratory syndrome coronavirus (SARSCoV), which appeared in 2002, and Middle East respiratory syndrome coronavirus (MERS-CoV), which was reported in 2012 [2]. Since the virus is spreading worldwide, on March 11, 2020, the WHO officially described the COVID-19 outbreak as a pandemic.

Virion structure and its genome:

Coronaviruses are structurally enveloped, belonging to the positive-strand RNA virus's category that has the largest known genomes of RNA. The structures of the coronavirus are more spherical in shape, but their structure has the potential to modify their morphology in response to environmental conditions, being pleomorphic. The capsular membrane which represents the outer envelope usually has glycoprotein projection and covers the nucleus, comprising a matrix protein containing a positive-strand RNA. Since the structure possesses 5'-capped and 3'polyadenylated ends, it remains identical to the cellular mRNAs.[3] The structure is comprised of hemagglutinin esterase (HE) (present only in some beta-coronaviruses), spike (S), small membrane (E), membrane (M) and nucleocapsid (N), as shown (Figure 1). The envelope containing glycoprotein is responsible for attachment to the host cell, which possesses the primary anti-genic epitopes mainly those recognized by neutralizing antibodies. The spike S protein being in a spike form is subjected to a structural rearrangement process so that fusing the outer membrane of the virus with the host-cell membrane becomes easier. Recent SARS-CoV work has also shown that the membrane exopeptidase ACE enzyme (angiotensin-converting enzyme) functions as a COVID-19 receptor to enter the human cell.[4]

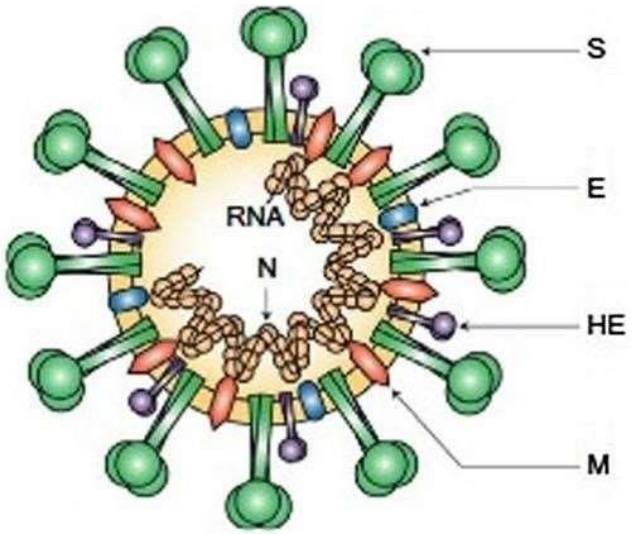

Figure 1.Virion structure and its genome

II. HISTORY

Coronaviruses are enveloped positive sense RNA viruses ranging from 60 nm to 140 nm in diameter with spike like projections on its surface giving it a crown like appearance under the electron microscope; hence the name coronavirus [5]. Four corona viruses namely HKU1, NL63, 229E and OC43 have been in circulation in humans, and generally cause mild respiratory disease. There have been two events in the past two decades wherein crossover of animal beta corona viruses to humans has resulted in severe disease. The first such instance was in 2002– 2003 when a new coronavirus of the β genera and with origin in bats crossed over to humans via the intermediary host of palm civet cats in the Guangdong province of China. This virus, designated as severe acute respiratory syndrome coronavirus affected 8422 people mostly in China and Hong Kong and caused 916 deaths (mortality rate 11%) before being contained [6]. Almost a decade later in 2012, the Middle East respiratory syndrome coronavirus (MERS-CoV), also of bat origin, emerged in Saudi Arabia with dromedary camels as the intermediate host and affected 2494 people and caused 858 deaths (fatality rate 34%) [7].

III. ORIGIN AND SPREAD OF COVID-19

In December 2019, adults in Wuhan, capital city of Hubei province and a major transportation hub of China started presenting to local hospitals with severe pneumonia of unknown cause. Many of the initial cases had a common exposure to the Wuhan wholesale seafood market that also traded live animals. The surveillance system (put into place after the SARS outbreak) was activated and respiratory samples of patients were sent to reference labs for etiologic investigations. On December 31st 2019, China notified the outbreak to the World Health Organization and on 1st January the Wuhan sea food market was closed. On 7th January the virus was identified as a coronavirus that had >95% homology with the bat coronavirus and > 70% similarity with the SARS-CoV. Environmental samples from the Wuhan sea food market also tested positive, signifying that the virus originated from there [9]. The number of cases started increasing exponentially, some of which did not have exposure to the live animal market, suggestive of the fact that human-to-human transmission was occurring [10]. The first fatal case was reported on 11th Jan 2020. The massive migration of Chinese during the Chinese New Year fueled the epidemic. Cases in other provinces of China, other countries (Thailand, Japan and South Korea in quick succession) were reported in people who were returning from Wuhan.

Transmission to healthcare workers caring for patients was described on 20th Jan, 2020. By 23rd January, the 11 million population of Wuhan was placed under lock down with restrictions of entry and exit from the region. Soon this lock down was extended to other cities of Hubei province. Cases of COVID-19 in countries outside China were reported in those with no history of travel to China suggesting that local human-to-human transmission was occurring in these countries [11]. Airports in different countries including India put in screening mechanisms to detect symptomatic people returning from China and placed them in isolation and testing them for COVID-19. Soon it was apparent that the infection could be transmitted from asymptomatic people and also before onset of symptoms. Therefore, countries including India who evacuated their citizens from Wuhan through special flights or had travelers returning from China, placed all people symptomatic or otherwise in isolation for 14 d and tested them for the virus.

Cases continued to increase exponentially and modelling studies reported an epidemic doubling time of 1.8 d [12]. In fact, on the 12th of February, China changed its definition of confirmed cases to include patients with negative/ pending molecular tests but with clinical, radiologic and epidemiologic features of COVID-19 leading to an increase in cases by 15,000 in a single day [8]. As of 05/03/2020 96,000 cases worldwide (80,000 in China) and 87 other countries and 1 international conveyance (696, in the cruise ship Diamond Princess parked off the coast of Japan) have been reported. It is important to note that while the number of new cases has reduced in China lately, they have increased exponentially in other countries including South Korea, Italy and Iran. Of those infected, 20% are in critical condition, 25% have recovered, and 3310 (3013 in China and 297 in other countries) have died [13]. India, which had reported only 3 cases till 2/3/2020, has also seen a sudden

spurt in cases. By 5/3/2020, 29 cases had been reported; mostly in Delhi, Jaipur and Agra in Italian tourists and their contacts. One case was reported in an Indian who traveled back from Vienna and exposed a large number of school children in a birthday party at a city hotel. Many of the contacts of these cases have been quarantined.

These numbers are possibly an underestimate of the infected and dead due to limitations of surveillance and testing. Though the SARS-CoV-2 originated from bats, the intermediary animal through which it crossed over to humans is uncertain. Pangolins and snakes are the current suspects.

IV. CLINICAL AND PATHOLOGICAL CHARACTERISTICS OF COVID-19

SARS-CoV-2 targets the respiratory system, and transmission occurs via contact droplets and fomites from an infected person who may be symptomatic or asymptomatic. During the incubation period, the virus triggers a slow response in the lungs. SARS-CoV-2 mainly invades alveolar epithelial cells, resulting in respiratory symptoms.

The S-glycoprotein on the surface of SARS-CoV-2 binds to ACE2. The receptor and the enzyme on the surface of type 2 alveolar cells induce a conformational change in S-glycoprotein initiating proteolytic digestion by host cell proteases (TMPRSS2 and furin), ultimately leading to internalization of the virion. This implies that SARS-CoV-2 has a pathogenesis similar to that of SARS-CoV. Coronaviruses generally enter via endocytosis or direct fusion of the viral envelope with the host membrane. Once internalized by the host cell, the viral particle is uncoated, and its genome enters the cell cytoplasm. Coronaviruses have an RNA genome from which they can directly produce their proteins and new genomes in the cytoplasm by attaching to the host ribosomes [14]. The host ribosomes translate viral RNA into RNA polymerase proteins. This RNA polymerase then reads the positive strand again to generate single-stranded, negative-sense RNA (ssRNA-) strands. The ssRNA- strands are then used as a template by RNA polymerase to make additional ssRNA+ strands. The small RNA strands are read by host ribosomes in the endoplasmic reticulum to make the structural components of the virus. These structural components are then transferred from the endoplasmic reticulum to the Golgi apparatus. Within the Golgi apparatus, ssRNA+ genomes are packaged in the nucleocapsids to create new virion particles. These progeny viruses are then released from the host cell via exocytosis through secretory vesicles. The replication of the virus in alveolar cells mediates damage and induces an inflammatory response in the tissues. Cellular entry of the virus triggers an inflammatory response by recruiting T-helper cells that produce interferon (IFN)-gamma (IFN-γ), interleukin (IL)-2, and IL-12. The injured alveolar cells also release interferons, cytokines, and other intracellular components. The subsequent recruitment of other inflammatory cells leads to the development of a 'cytokine storm' which can precipitate the organ damage and multi-organ failure seen in severe disease [14]. COVID-19 infected patients have shown higher concentrations of peripheral blood immune mediators. IL-6, interferon gamma-induced protein (IP)-10, and IFN-γ were markedly elevated in all three highly pathogenic HCoV infections. Interferons act in a paracrine manner and can have numerous effects on the surrounding cells, preparing them against viral infection. The alveolar macrophages detect cell injury and respond to cytokines released by injured alveolar cells. The alveolar macrophages respond by secreting cytokines and chemokines. The inflammatory process occurring within the lung parenchyma stimulates nerve endings responsible for initiating the cough reflex, thus, people often present with an early dry cough. Tumor necrosis factor (TNF)-α and IL-1β are proinflammatory cytokines that cause an increase in vascular permeability, increase in adhesion molecule expression, and induce recruitment of more immune cells, including neutrophils and monocytes. They bind to adhesion proteins on the surface of tissues and enter the site of injury. IL-8 recruits neutrophils, and other chemokines attract monocytes [15]. The increase in vascular permeability causes leakage of fluid into the interstitial space and alveoli, resulting in interstitial and pulmonary edema. This can lead to dyspnea, impaired oxygenation, or hypoxemia.

V. EPIDEMIOLOGY AND PATHOGENESIS

All ages are susceptible. Infection is transmitted through large droplets generated during coughing and sneezing by symptomatic patients but can also occur from asymptomatic people and before onset of symptoms. Studies have shown higher viral loads in the nasal cavity as compared to the throat with no difference in viral burden between symptomatic and asymptomatic people. Patients can be infectious for as long as the symptoms last and even on clinical recovery. Some people may act as super spreaders; a UK citizen who attended a conference in Singapore infected 11 other people while staying in a resort in the French Alps and upon return to the UK [8]. These infected droplets can spread 1–2 m and deposit on surfaces. The virus can remain viable on surfaces for days in favorable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. Infection is acquired either by inhalation of these droplets or touching surfaces contaminated by them and then touching the nose, mouth and eyes. The virus is also present in the stool

and contamination of the water supply and subsequent transmission via aerosolization/feco oral route is also hypothesized. As per current information, trans placental transmission from pregnant women to their fetus has not been described [16]. However, neonatal disease due to post-natal transmission is described. The incubation period varies from 2 to 14 d [median 5 d]. Studies have identified angiotensin receptor 2 (ACE_2) as the receptor through which the virus enters the respiratory mucosa [17].

The basic case reproduction rate (BCR) is estimated to range from 2 to 6.47 in various modelling studies [17]. In comparison, the BCR of SARS was 2 and 1.3 for pandemic flu H1N1 2009.

VI. CLINICAL FEATURES

The clinical features of COVID-19 are varied, ranging from asymptomatic state to acute respiratory distress syndrome and multi organ dysfunction. The common clinical features include fever (not in all), cough, sore throat, headache, fatigue, headache, myalgia and breathlessness. Conjunctivitis has also been described. Thus, they are indistinguishable from other respiratory infections. In a subset of patients, by the end of the first week the disease can progress to pneumonia, respiratory failure and death. This progression is associated with extreme rise in inflammatory cytokines including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1A, and TNFα [18]. The median time from onset of symptoms to dyspnea was 5 d, hospitalization 7 d and acute respiratory distress syndrome (ARDS) 8 d. The need for intensive care admission was in 25–30% of affected patients in published series. Complications witnessed included acute lung injury, ARDS, shock and acute kidney injury. Recovery started in the 2nd or 3rd wk. The median duration of hospital stays in those who recovered was 10 d. Adverse outcomes and death are more common in the elderly and those with underlying co-morbidities (50–75% of fatal cases). Fatality rate in hospitalized adult patients ranged from 4 to 11%. The overall case fatality rate is estimated to range between 2 and 3%.

Interestingly, disease in patients outside Hubei province has been reported to be milder than those from Wuhan [19]. Similarly, the severity and case fatality rate in patients outside China has been reported to be milder [8]. This may either be due to selection bias wherein the cases reporting from Wuhan included only the severe cases or due to predisposition of the Asian population to the virus due to higher expression of ACE_2 receptors on the respiratory mucosa.

Disease in neonates, infants and children has been also reported to be significantly milder than their adult counterparts. In a series of 34 children admitted to a hospital in Shenzhen, China between January 19th and February 7th, there were 14 males and 20 females. The median age was 8 years and in 28 children the infection was linked to a family member and 26 children had history of travel/residence to Hubei province in China. All the patients were either asymptomatic (9%) or had mild disease. No severe or critical cases were seen. The most common symptoms were fever (50%) and cough (38%). All patients recovered with symptomatic therapy and there were no deaths. One case of severe pneumonia and multiorgan dysfunction in a child has also been reported. Similarly, the neonatal cases that have been reported have been mild [20].\

VII. DIAGNOSIS

A suspect case is defined as one with fever, sore throat and cough who has history of travel to China or other areas of persistent local transmission or contact with patients with similar travel history or those with confirmed COVID-19 infection. However, cases may be asymptomatic or even without fever. 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 Broncho alveolar 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 do not 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 nonspecific. 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 CT scans 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 [21].

VIII. TREATMENT

Treatment is essentially supportive and symptomatic.

The first step is to ensure adequate isolation (discussed later) to prevent transmission to other contacts, patients and healthcare workers. Mild illness should be managed at home with counseling about danger signs. The usual principles are maintaining hydration and nutrition and controlling fever and cough. Routine use of antibiotics and antivirals such as oseltamivir should be avoided in confirmed cases. In hypoxic patients, provision of oxygen through nasal prongs, face mask, high flow nasal cannula (HFNC) or non-invasive ventilation is indicated. Mechanical ventilation and even extra corporeal membrane oxygen support may be needed. Renal replacement therapy may be needed in some. Antibiotics and antifungals are required if coinfections are suspected or proven. The role of corticosteroids is unproven; while current international consensus and WHO advocate against their use, Chinese guidelines do recommend short term therapy with low-to-moderate dose corticosteroids in COVID-19 ARDS [21]. Detailed guidelines for critical care management for COVID-19 have been published by the WHO. There is, as of now, no approved treatment for COVID-19. Antiviral drugs such as ribavirin, lopinavirritonavir have been used based on the experience with SARS and MERS. In a historical control study in patients with SARS, patients treated with lopinavir-ritonavir with ribavirin had better outcomes as compared to those given ribavirin alone.

In the case series of 99 hospitalized patients with COVID-19 infection from Wuhan, oxygen was given to 76%, non-invasive ventilation in 13%, mechanical ventilation in 4%, extracorporeal membrane oxygenation (ECMO) in 3%, continuous renal replacement therapy (CRRT) in 9%, antibiotics in 71%, antifungals in 15%, glucocorticoids in 19% and intravenous immunoglobulin therapy in 27% [22]. Antiviral therapy consisting of oseltamivir, ganciclovir and lopinavirritonavir was given to 75% of the patients. The duration of non-invasive ventilation was 4–22 d [median 9 d] and mechanical ventilation for 3–20 d [median 17 d]. In the case series of children discussed earlier, all children recovered with basic treatment and did not need intensive care.

There is anecdotal experience with use of remdeswir, a broad spectrum anti RNA drug developed for Ebola in management of COVID-19. More evidence is needed before these drugs are recommended. Other drugs proposed for therapy are arbidol (an antiviral drug available in Russia and China), intravenous immunoglobulin, interferons, chloroquine and plasma of patients recovered from COVID-19. Additionally, recommendations about using traditional Chinese herbs find place in the Chinese guidelines [23].

IX. PREVENTION

The CDC recommends multiple steps to prevent the transmission and risk of SARS-CoV-2. Frequent hand washing lasting at least 20 seconds by using soap and water is advised. Hand sanitizers with at least 60% alcohol can also be used as an alternative. The public has also been told to avoid touching mucosal surfaces such as the mouth and the nose with hands that have not been washed. Anyone showing symptoms of the virus should try to seek appropriate medical help. They should also limit their exposure to other unaffected people and cover their noses and mouths when coughing or sneezing. They are also advised to wear a facemask if they present with symptoms. Frequent disinfection and cleaning are advised for groups that are at risk of contracting the virus [24].

X. CONCLUSIONS

This new virus outbreak has challenged the economic, medical and public health infrastructure of China and to some extent, of other countries especially, its neighbor's. Time alone will tell how the virus will impact our lives here in India. More so, future outbreaks of viruses and pathogens of zoonotic origin are likely to continue. Therefore, apart from curbing this outbreak, efforts should be made to devise comprehensive measures to prevent future outbreaks of zoonotic origin.

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