

A Review of Pathogenesis, Treatment and Prevention of Novel Corona Virus (SARS-CoV-2)

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Abstract

A recent outbreak of highly transmissible and pathogenic virus SARS-CoV-2 with severe acute respiratory syndrome have emerged in humans in this 21st century in China. On 11th March 2020, the World Health Organization (WHO) announced it as a pandemic which has to be brought to global attention. Extensive prophylactic measures for reduction of the transmission of SARS-CoV-2 from one person to another and to control the current outbreak has been implemented. Special care and effort are to be given to protect or minimize transmission of infection among susceptible populations, healthcare professionals, children and the elderly. So far no specific therapies and vaccines to control the SARS-CoV-2. This review highlights on history of emergence, genomic diversity, pathogenesis, clinical characteristics, transmission, treatments and prevention of SARS-CoV-2 and WHO guidelines to healthcare staff in order to manage the outbreak clinically.

Keywords: Corona Virus; SARS-CoV-2; Pandemic; Treatment; Prevention

Abbreviations

CoV: Coronavirus; HCoVs: Human Coronaviruses; SARS-CoV-2: Coronavirus Disease 2019; 2019-nCoV: Novel Coronavirus; SARS-CoV: Severe Acute Respiratory Syndrome Coronavirus; MERS-CoV: Middle East Respiratory Syndrome Coronavirus; ACE2: Angiotensin-Converting Enzyme 2 (ACE2); WHO: World Health Organization; CDC: Centers for Disease Control and Prevention, Atlanta, US; PPE: Personal Protective Equipment

Introduction

Coronavirus considered initially as a major endemic pathogen, causes severe acute respiratory syndrome SARS -CoV-2 [1]. It is a major threat to public health and have a very high fatality rate. In December 31, 2019, a large number of cases in a private hospital, Wuhan, Hubei, China reported a type of pneumonia, a highly infectious disease [2].

The etiology of that pneumonia was unknown and later the novel coronavirus (2019-nCoV) was identified as the causative agent. It is an ongoing outbreak and has been declared a global emergency by the WHO [3,4]. The virus has now been named SARS-CoV-2 (International Committee for Virus Taxonomy - ICTV). This virus is responsible for the global outbreak and currently it was documented by WHO as COVID-19. SARS-CoV-2 pneumonia was first reported in Wuhan on 1st January 2020 [5].

The patient with suspected COVID infection in Wuhan were related epidemiologically to wholesale market of seafood and wet animal. Due to a suspected relationship with this outbreak, the authorities of public health in Wuhan have shut down the market where live and wild animals were sold out January 1st 2020 [6]. As predicted, Center for Disease Control and Prevention (CDC) has isolated SARS-CoV-2 in China from the environmental samples of the Wuhan Seafood Market, suggesting the origin of the outbreak [7,8].

Novel Corona virus SARS-CoV-2 was isolated by the researchers rapidly from infected pneumonia patients on January 7, 2020 [2]. Identification of the virus was done by real-time reverse transcription polymerase chain reaction (RT-PCR) and next generation sequencing. The first case was reported in 2019 (December). Since, December 18th to 29th (2019) nearly five patients with ARDS were hospitalized and one died. Further, on January 30th 2020, the first case of SARS-CoV-2 with human-to-human transmission was documented in US [9].

WHO strategic objectives [10]:

- Disruption of human-to-human transmission together with reduction of secondary infections among close contacts and health-care professionals.
- Prevention of transmission amplification and further global spread.
- Identify, isolate and treat early patients, including optimized care for patients who have been infected.
- Identify and decrease transmission from the animal source.
- Consign critical unknowns regarding therapeutic severity, extent of transmission and infection, potential treatments.
- Hasten the diagnostic, therapeutic and vaccine development.

These strategies can be achieved by combining public health measures such as:

- Rapid identification, diagnosis of patients and their treatment
- Contact identification and follow-up
- The prevention and control of health-care infections
- Implementation of health care measures for travellers
- Population awareness regarding the risk of infection and their social distancing.

The documented symptoms, pathogenesis, clinical characteristics and treatments of SARS-CoV-2 cases were analyzed to help the health workers worldwide in order to fight against the current outbreak.

Coronavirus virion morphology

Coronavirus is a single-stranded, positive-sense RNA virus enveloped, non-segmented with genome size 29.9 kb. Nucleocapsid of virion encloses the phosphorylated nucleocapsid (N) protein and genomic RNA, embedded in bilayers of phospholipid and protected with

glycoprotein trimmer (S) spike. The S proteins in the virus envelope has a M- membrane protein, E- envelope protein and HE- hemagglutinin-esterase (Figure 1).

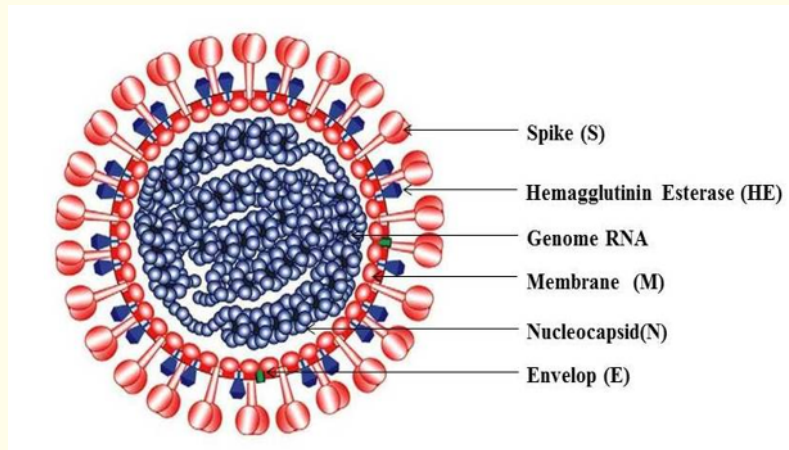


Figure 1: Coronavirus virion morphology.

Classification

Clinicians found SARS had emerged a few months ago as two strains before SARS-CoV-2 was documented. A recent phyloepidemiological report indicates that SARS-CoV-2 may have been imported from other Huanan Seafood Market locations [11]. To date, the origins of SARS-CoV-2 remain unknown, epidemiological and etiological studies are being carried out by the Chinese health authorities. Isolation of the SARS-CoV-2 was first from three SARS-COV-2 patient in there Bronchoalveolar Lavage Fluid (BALF) at Wuhan Jinyintan Hospital on 30 December 2019 [12]. SARS-CoV-2 was found to be associated as SARS-COV-2 virus after sequencing and evolutionary tree research analysis. These viruses can cause neurological, hepatic, intestinal and respiratory illnesses [13] (Figure 2).

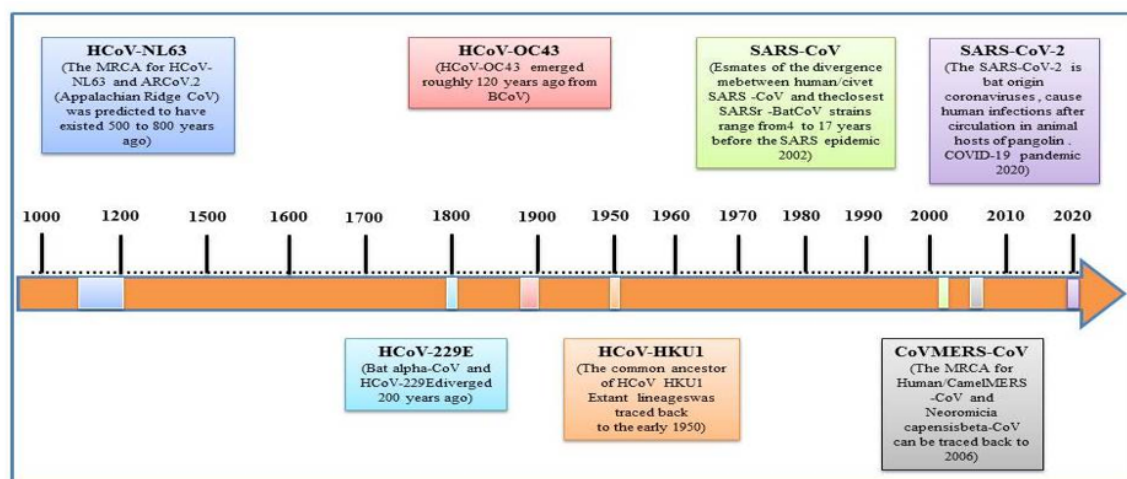


Figure 2: A timeline for the emergence of HCoVs.

Note: HCoV-229E and HCoV-NL63 were dated approximately 500 - 800 years ago and 200 years ago, respectively. About 120 years ago, HCoV-OC43 was believed to have a common ancestor with BCoV. The MRCA of the current lines of HCoV-HKU1 was calculated to have occurred in the 1950s. Molecular dating studies calculated that SARS-CoV and MERS-CoV differed from batCoVs in 2002 and 2006. Finally, SARS-CoV-2 is bat coronavirus, which causes human infections in animal hosts of pangolin after circulation. COVID-19 is a 2020 pandemic.

Genome diversity

Various CoVs exhibit diverse host range and tropism of tissue. The CoVs are serologically and genotypically divided into four subfamilies, Mammals typically get infected by alphacoronaviruses, betacoronaviruses, gammacoronaviruses and deltacoronaviruses infect fish, birds and rarely infect mammals too. There were only six CoV which were proved to infect the humans with respiratory illnesses before 2019.

HCoV-229E, HCoV-NL63 HKU1 and HCoV-OC43, were known to cause mild upper respiratory infections and rarely severe infection in babies, young children and elderly. SARS-CoV as well as the MERS-CoV invaded the lower respiratory tract with severe breathing syndrome in humans [14,15]. Genome-wide phylogenetic study suggests that SARS-CoV-2 shares the identity of 80%, 50% with SARS-CoV and MERS-CoV respectively [16]. The novel CoV, 2019-novel coronavirus of betacoronaviruses, infects the lower respiratory tract with pneumonia in humans however the symptoms tend to be milder than the earlier SARS and MERS [2]. Clinical diagnosis, epidemiological investigations and sequence analysis confirmed from 291 cases in China; includes 270 Wuhan cases and 21 in Beijing, Shanghai and Guangdong.

Transmission

On 30th January 2020 the disease was declared has a global significance and public health emergency. This advice suggests that each nation needs to do a lot in terms of their preparation to respond to the sudden emergence of cases within its national boundaries [17]. This is likely to be a zoonotic origin for those infected people who have been exposed to Wuhan City's wet animal market where live animals are regularly sold. Genomic sequence analysis of SARS-CoV-2 revealed to have 88% similar identification with two extreme bat-derived and recent coronaviruses with the intermediate carriers and host reservoir for the spread of infection to humans [18].

Studies have shown that 2019-nCoV is effectively transmitted from person to person, even during the isolation efforts at medical institutions. The most serious threat was the transmission in health-care settings. In recent case scenarios, 57 (41%) of 138 patients reported infection from health care settings, along with 40 (29%) healthcare workers [19]. While further research is required, to prove that asymptomatic persons could also appear to be the probable sources of 2019-nCoV infection. Several reports documented the transmission of SARS-CoV-2 infection and spread is by person to person [20]. This is supported by cases that occur in families and between people who have not visited the wet animal market in Wuhan Transmission from one person to another occurs primarily through droplets spread coughing, sneezing and direct contact from an infected person [21].

Incubation period

Clinical characteristics of SARS-CoV-2 occurred after an incubation time of approximately < 5.2 days. The period from the onset of SARS-CoV-2 symptoms to death ranged from 6 to 41 days, with a median of 14 days. This time period depends on the age of the patient and the status of the immune system [9]. Among patients > 70 years of age it was found to be shorter especially those who are on mechanical ventilation.

Immune response

In COVID 19 infected patients were reported to have significantly high levels of cytokines and chemokines in the blood including IL1- β , IL1RA, IL6, IL7, IL8, IL9, IL10. Many of the severe cases admitted to the intensive care unit reported elevated levels of pro-inflammatory cytokines, including IL2, IL7, IL10, GCSF, IP10, MCP1, MIP1 α , and TNF α , which were reasoned to increase the severity of the disease [22].

In certain cases, peripheral ground-glass opacities due to systemic and localized immune response in both sub-pleural regions of the lungs lead to increased inflammation.

Pathogenesis

Viral replication initially occurs in the upper respiratory tract, pharynx and nasal cavity mucosal epithelium and multiplication takes place in the lower respiratory tract as well as gastrointestinal mucosa leading to mild viremia [23]. Some infected patients remain asymptomatic at this point. Some showed non pulmonary symptoms involving multi-organ failure like acute liver failure, kidney failure, cardiac injury, gastrointestinal with diarrhea [24].

Human epidemics and pandemics were caused from 2003 and 2012 by severe acute respiratory coronavirus syndrome (SARS-CoV) and Middle East coronavirus respiratory syndrome (MERS-CoV) respectively [25]. In certain ethnic groups, SARS-CoV has a much higher mortality. Both these viruses are potent inducer of cytokine inflammation. The predicated organ damage mechanism is the “cytokine storm” and is also known as cytokine cascade”.

Angiotensin-Converting Enzyme 2 (ACE2) is commonly expressed in nasal mucosa, bronchus, lung, heart, esophagus, kidney, stomach, bladder and ileum and they are all vulnerable to SARS-CoV-2 and similar to SARS- CoV infection. The initial onset of rapid viral replication may cause massive epithelial and endothelial cell death and vascular cell leakage, triggering the production of exuberant pro-inflammatory cytokines and chemokines.

Loss of pulmonary ACE2 function has been proposed to be related to acute lung injury because ACE2 down- regulation and shedding can lead to dysfunction of the renin-angiotensin system (RAS) and further enhance inflammation and cause vascular permeability. Rapid viral replication and cellular damage, virus-induced ACE2 down-regulation, shedding and antibody dependent enhancement (ADE) are responsible for aggressive inflammation caused by SARS-CoV-2.

Clinicians have also recently suggested potential pathogenicity in fertility concerns among the young patients by SARS-CoV-2 infection due to damage in the testicular tissues. The first step is binding to a receptor with virus, expressed by host cells which are followed later by the cell membrane fusion. The virus’ initial target is lung epithelial cells. Basically, the receptor-binding domain sequence of SARS CoV and SARS-CoV-2 are similar [24]. These data strongly suggest that host cells are most likely entered through the ACE2 receptor. The main routes of transmission are currently considered to be respiratory droplets and contact transmission. Recent reports indicate that even in the stools and urine of patients suffering SARS-CoV-2 can be detected, thus increasing the risk of fecal oral transmission. Certain literature documented that ingestion of virus-contaminated food may cause infection and transmission [26] (Figure 3).

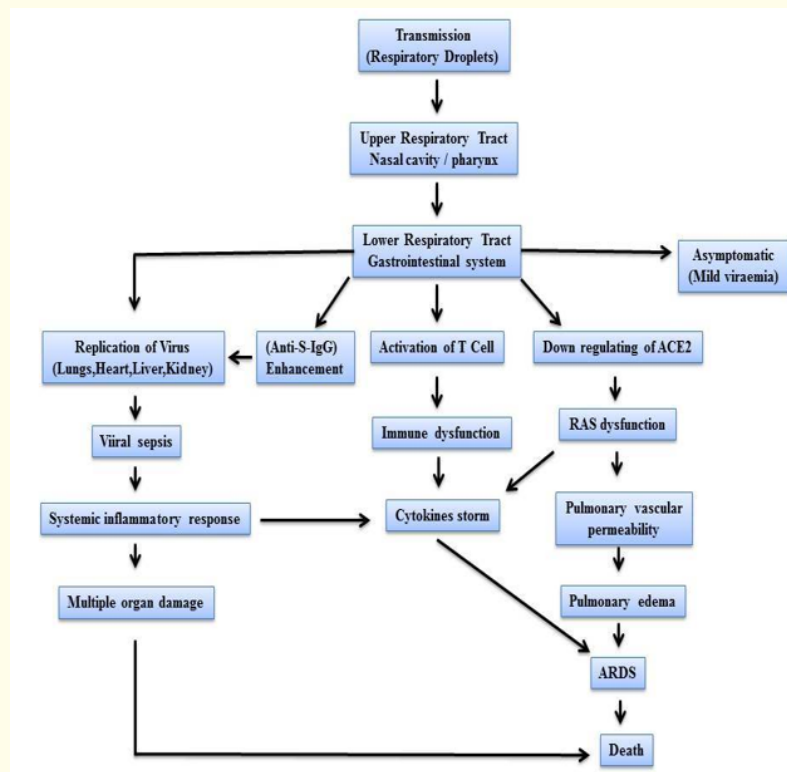


Figure 3: The pathogenesis of SARS-CoV-2.

Note: Pathogenesis of SARS-CoV-2 infection. ACE2: Angiotensin Converting Enzyme 2; RAS: Renin Angiotensin System; ARDS: Acute Respiratory Distress Syndrome.

Symptoms and clinical features

Huang, *et al.* first reported clinical features of 41 patients confirmed to be infected with COVID-19 on January 2, 2020, which include 13 ICU cases and 28 non-ICU cases. More than half of the cases (66%) had been exposed to the Huanan Seafood Wholesale Market [27,28]. The initial symptoms were with sputum (28%), cough (76%), fever (98%), dyspnea (55%), weakness (44%), diarrhoea (3%) and hemoptysis (5%). Five (12%) patients experienced acute heart injury [29].

SARS-CoV-2, however, showed some uncommon clinical characteristics targeting the lower respiratory tract combined with few severe symptoms of the upper respiratory tract such as rhinorrhea, sneezing and sore throat [30]. Chest X-rays showed infiltration in the upper lobe of the lung with dyspnea with hypoxemia. Severe symptoms are associated with increasing incidence and death rates particularly in the United States, Italy, Germany, and China epidemic area. Patients with SARS-CoV-2 may have higher leukocyte counts, irregular respiratory findings and elevated plasma-pro-inflammatory cytokine levels [31].

Huang *et al.*, reported clinical cases as three (7%) were suffering from shock, twelve (29%) with ARDS, three (7%) with acute kidney injury [28]. Chen, *et al.* had documented 99 cases of pneumonia infected with SARS-CoV-2. One patient of SARS-CoV-2 case reported with cough, difficulty breathing with 5 days of fever [27]. Severe pneumonia was the major pathogenesis of SARS-CoV-2 infection, combined with the occurrence of ground-glass opacity and acute cardiac injury as a virus in the respiratory system [32].

Treatment

The transmission of SARS-CoV-2 infection from person to person has led to a range of treatments being given in patient isolation. There are no specific vaccine and antiviral drugs for potential treatment of SARS-CoV-2 infections in humans. Most treatment is symptomatic and supportive with anti-inflammatory, antiviral and invasive mechanical ventilation treatments [33].

In the United States, the first patient reported a 2019-nCoV infection was treated with remdesivir and other antiretrovirals, similar to ritonavir [34]. The course of treatment included oral administration of 500 mg of lopinavir twice daily, 75 mg of oseltamivir, 500 mg of ritonavir and 0.25g of ganciclovir for intravenous administration 3 - 14 days. The antiviral remdesivir and chloroquine are highly effective combination in controlling *in vitro* infection with 2019-nCoV. A recent study with Baricitinib suggested this as a potential treatment drug in the hope of reducing both the virus invasion and the inflammation process [35].

For better understanding of the virus-host interactions, scientists are to initiate a non-human primate model that will study SARS-CoV-2 infection with an approach to developing rapid track novel therapies and testing potential vaccines. Recently it is recommended to use convalescent plasma for SARS-CoV-2 but the effect of convalescent plasma cannot be distinguished from the effects of patient comorbidity, disease stage or other therapeutic effects [36].

Documentation on SARS-CoV neutralization of the monoclonal antibody (mAb) and inhibition syncytia formation between the cells expressing the S protein and those expressing the SARS-CoV receptor ACE2 was reported. However, only one epitope is recognizable by mAbs and the anti-infective effect may be limited. In addition, the initiation of the use of mAbs involves a certain period of time which is impossible to achieve in this current short period of time in clinical application [37]. According to WHO's recent update, eight SARS-CoV-2 vaccine candidates are right now in the human trial phase. Four of these are from China, three from the USA, and one from the UK. Of eight, seven are in phase 1 and 2 of trials.

Vaccine and prevention

For SARS-CoV-2 controls, vaccination is likely the best option. Protein-RBD vaccines were widely proposed and started based on epitope structure, mRNA and Spike. SARS-CoV-2 has been reported to have been rapidly reconstructed using a synthetic genomics platform

and this technical advance is useful for the development of the vaccines. Human ACE2 transgenic mouse and rhesus monkey SARS-CoV-2 models for vaccine research have been well established and some SARS-CoV-2 vaccines are already under clinical trial.

The current outbreak SARS-CoV-2 by spreading from person to person has to be controlled [13,38]. Special attention and efforts to protect susceptible children, health care providers and elderly people are needed. All travelers are advised to avoid close contact with people who have already had acute respiratory infections (ARI). China and other countries have implemented extensive prevention and control steps to monitor further virus spread including travel screening [19].

Individuals present with ARI symptoms during or after travel, should seek medical attention and inform the health care professional about their travel history. Virus spread through physical contact with wet and contaminated items. It is possible to transmit the virus through the ocular surface, so eye safety should be followed. Hand-washing is the main viral safety precautions. It also recommends the use of masks, gowns and gloves. The public utilities and facilities are provided with routine, periodic hourly decontamination and hand washing reagents (PPE and social distancing) [39].

Conclusion

The Human CoVs' pandemic remains a major threat to public health and causes financial crisis around the world. WHO has suggested preventive measures to break the chain of disease transmission. Technical guidance as instructed and advised by the WHO has to be followed appropriately by the front-line workers to end this pandemic, as there are no specific antiviral drugs or vaccines till date. The current objective is to effectively reduce the incidence of cases and to control the global outbreak.

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