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Review Article

A critique of Coronavirus (COVID-19).

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ABSTRACT
Coronavirus is an enveloped, positive-sense, single-stranded RNA virus that is diversely found in humans and wildlife. They are known to infect the neurological, respiratory, enteric, and hepatic systems. The past few decades have seen endemic outbreaks in the form of middle east respiratory syndrome Coronavirus (MERS-CoV) and severe acute respiratory syndrome related coronavirus (SARS-CoV). Yet again, we see emergence of another outbreak due to a new strain called the SARS-CoV-2 virus. The most recent outbreak initially presented as pneumonia of unknown etiology in a cluster of patients in Wuhan, China. The epicenter of infection was linked to seafood and exotic animal wholesale markets in the city. SARS-CoV-2 is highly contagious and has resulted in a rapid pandemic of COVID-19. As the number of cases continues to rise, it is clear that these viruses pose a threat to public health. This review will introduce a general overview of coronavirus and describe the clinical features, evaluation, and treatment of COVID-19 patients. It will also provide a means to raise awareness among primary and secondary healthcare providers during the current pandemic. Furthermore, our review focuses on the most up-to-date clinical information for the effective management, prevention, and counseling of patients worldwide.

KEYWORDS
Coronavirus, COVID-19, Pneumonia.

1. INTRODUCTION

Coronaviruses are a group of large, enveloped, positive-sense, single-stranded RNA viruses belonging to the order Nidovirales, family Coronaviridae, and subfamily Coronavirinae. Twenty-six different species are known and have been divided into four genera (Alpha, beta, gamma and delta) characterized by different antigenic cross-reactivity and genetic makeup. Only the alpha- and beta coronavirus genera include strains pathogenic to humans[1]. Human coronaviruses (HCoVs) represent a major group of corona viruses (CoVs) associated with multiple respiratory diseases of varying severity, including common cold, pneumonia and bronchiolitis [2]. Today, HCoVs are recognized as one of the most rapidly evolving viruses owing to its high genomic nucleotide substitution rates and recombination [3]. Given the high prevalence and wide distribution of coronaviruses, their large genetic diversity as well as the frequent recombination of their genomes and increasing activity at the human animal interface, these viruses represent an ongoing threat to human[4]. This fact became evident in late 2019 and early 2020, when a novel coronavirus was discovered to be the cause of a large and rapidly spreading outbreak of respiratory disease, including pneumonia, in worldwide.

1.1. Epidemiology

In December 2019, many pneumonia cases that were clustered in Wuhan city were reported and searches for the source have shown Huanan Seafood Market as the origin[5]. The first case of the COVID-19 epidemic was discovered with unexplained pneumonia on December 12, 2019, and 27 viral pneumonia cases with seven being severe, were officially announced on December 31, 2019[6]. Etiologic investigations have been performed in patients who applied to the hospital due to similar viral pneumonia findings. The common history of high-risk animal contact in the medical histories of these patients has strengthened the likelihood of an infection transmitted from animals to humans[6, 7].

On January 22, 2020, novel CoV has been declared tobe originated from wild bats and belonged to Group 2 of beta-coronavirus that contains Severe Acute Respiratory Syndrome Associated Coronavirus (SARS-CoV). Although COVID-19 and SARS-CoV belong to the same beta coronavirus subgroup, similarity at genome level is only 70%, and the novel group has been found to show genetic differences from SARS-CoV[8].

1.2. Taxonomy, Genomic Structure of Coronavirses

CoVs are a group of large enveloped RNA viruses under the Coronaviridae family. Together with Artierivirdae and Roniviridae, Coronaviridae is classified under the Nidovirale order [9]. As proposed by the International Committee for Taxonomy of Viruses, CoVs are further categorized into four main genera, Alpha-, Beta-, Gamma- and Delta coronaviruses based on sequence comparisons of entire viral genomes [10, 11]. These CoVs can infect a wide variety of hosts, including avian, swine and humans. HCoVs are identified to be either in the Alpha- or Beta coronavirus genera, including Alpha coronaviruses, HCoV-229E and HCoV-NL63, and Beta coronaviruses, HCoV-HKU1, SARS-CoV, MERS-CoV and HCoV-OC43.

Under the electron microscope, the CoV virions appear to be roughly spherical or moderately pleomorphic, with distinct "club-like" projections formed by the spike (S) protein [12,13,14] (Figure 1). Within the vision interior lies a helically symmetrical nucleo capsid that encloses a single-stranded and positive sense RNA viral genome of an extraordinarily large size of about 26 to 32 kilo bases [9] (Figure 2).

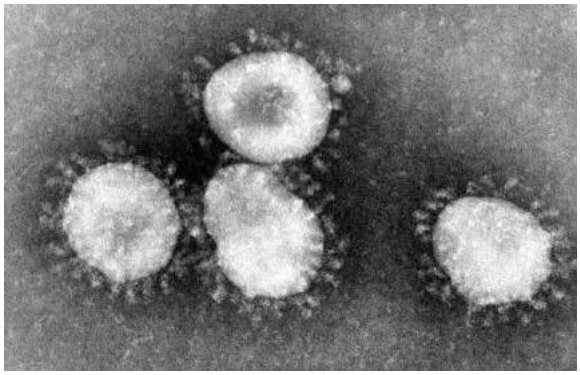

Fig. 1. Transmission electron micrograph of avian infectious bronchitis virus.

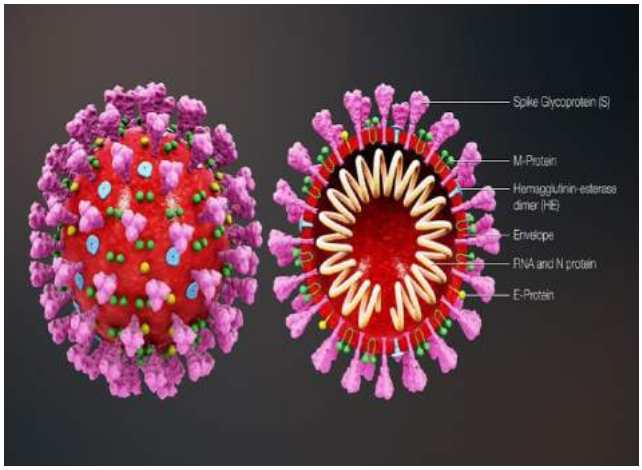

Fig. 2. Cross sectional model of a coronavirus.

The positive sense viral genomic RNA acts as a messenger RNA (mRNA), comprising a 51 terminal cap structure and a 31 poly a tail. This genomic RNA acts in three capacities during the viral life cycle: (1) as an initial RNA of the infectious cycle; (2) as a template for replication and transcription; and (3) as a substrate for packaging into the progeny virus. The replicate-transcriptase is the only protein translated from the genome, while the viral products of all downstream open reading frames are derived from sub genomic RNAs. In all CoVs, the replicate gene makes up approximately 51 two-thirds of the genome and is comprised of two overlapping open reading frames (ORFs), ORF1a and ORF1b, which encodes 16 non-structural proteins. The

final one-third of the CoV genomic RNA encodes CoV canonical set of four structural protein genes, in the order of spike (S), envelope (E), membrane (M) and nucleo capsid (N). In addition, several accessory ORFs are also interspersed along the structural protein genes and the number and location varies among CoV species [15] (Figure 3).

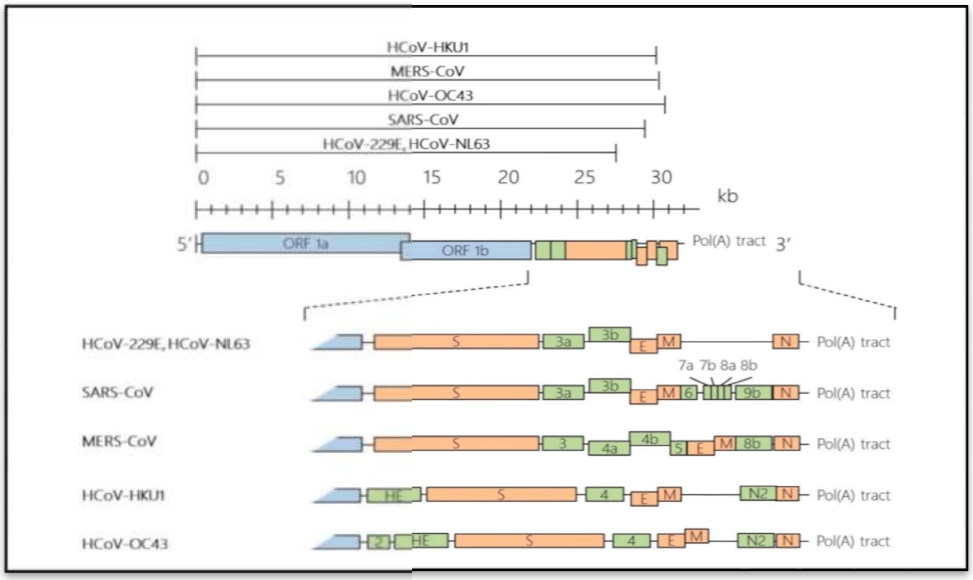

Fig. 3. Genome organization of human coronaviruses (HCoVs).

HCoV genomes range from about 26to 32 kilobases (kb) in size, as indicated by the black lines above the scale. Coronavirus (CoV) genome is typically arranged in the order of 51-ORF1a-ORF1b-S-E-M-N-31. The overlapping open reading frames (ORF) ORF1a and ORF1b comprise two-thirds of the coronavirus genome, which encodes for all the viral components required for viral RNA synthesis. The other one-third of the genome at the 31 endencodes for a set of structural (orange) and non-structural proteins (green).

1.3. Corona Virus: Life Cycle

Attack rates were higher than 50% in the healthcare setting during the outbreak, while household transmission was less efficient (6-8%) [16]. Simulation studies performed after the outbreak suggested that physicians and other health care workers were the principal vectors of SARS transmission in the hospital setting[17]. Practices such as use of ventilators and nebulized bronchodilators may cause aerosols and spread of droplets containing virus. The risk of spreading the virus may also be increased by cardio pulmonary resuscitation, bronchoscopy, endotracheal intubation, and airway and sputum suction[17]. Nosocomial spread was reduced through use of surgical masks, gloves and gowns. Virus load and shedding peak at approximately 10 days from the appearance of clinical symptoms, when the patient's status worsens and requires medical attention. Thus patients are most infectious at the time of seeking health care. [17]. Viral shedding continues for at least 13 more days (range 2-60 days). Patients are not infectious during the incubation period.

A few patients were identified as SARS "super spreaders" who spread the virus efficiently because they harbored above-normal levels of virus. A super spreading event was believed to be involved in the rapid propagation of the virus in the Amoy Gardens apartment building outbreak, where more than 300 residents were infected, presumably by a single patient. Other super spreading events were reported in the Hotel Metropole in Hong Kong, among passengers on Air China flight 112 from Hong Kong to Beijing, and in an acute care hospital in Toronto, Canada [18]. Super spreading seems to associate with high virus titer, aerosol generation, contamination of the environment, and close contact with others in a healthcare setting[17]. Viral RNA may persist long after serocon version, and could be detected in respiratory secretions, plasma and feces for some weeks [20].

1.4. Structure of Coronavirus

Coronavirus virions are spherical with diameters of approximately 125 nm as depicted in recent studies by cryo-electron tomography and cryo-electron microscopy [21, 22]. The most prominent feature of coronaviruses is the club-shape spike projections emanating from the surface of the vision. These spikes are a defining feature of the vision and give them the appearance of a solar corona, prompting the name, coronaviruses. Within the envelope of the vision is the nucleocapsid. Coronaviruses have helically symmetrical nucleocapsids, which is uncommon among positive-sense RNA viruses, but far more common for negative-sense RNA viruses.

Coronavirus virus particles contain four main structural proteins. These are the spike (S), membrane (M), envelope (E), and nucleocapsid (N) proteins, all of which are encoded within the 3′ end of the viral genome. The S protein (∼150 kDa), utilizes an N-terminal signal sequence to gain access to the ER, and is heavily N-linked glycosylated. Homodimers of the virus encoded S protein make up the distinctive spike structure on the surface of the virus [23, 24]. The trimeric S glycoprotein is a class I fusion protein and mediates attachment to the host receptor. In most, but not all, coronaviruses, S is cleaved by a host cell furin-like protease into two separate polypeptides noted S1 and S2. S1 makes up the large receptor-binding domain of the S protein while S2 forms the stalk of the spike molecule [25, 26, 27]. The M protein is the most abundant structural protein in the vision. It is a small (∼25–30 kDa) protein with 3 transmembrane domains and is thought to give the vision its shape. It has a small N-terminal glycosylated ectodomain and a much larger C-terminal end domain that extends 6–8 nm into the viral particle. Despite being co-translationally inserted in the ER membrane, most M proteins do not contain a signal sequence. Recent studies suggest the M protein exists as a dimer in the vision, and may adopt two different conformations allowing it to promote membrane curvature as well as bind to the nucleocapsid [28, 29]. The E protein (∼8–12 kDa) is found in small quantities within the vision. E protein from coronaviruses is highly divergent but has a common architecture. The membrane topology of E protein is not completely resolved but most data suggest that it is a transmembrane protein. The E protein has an N-terminal ectodomain and a C-terminal end domain and has ion channel activity. As opposed to other structural proteins, recombinant viruses lacking the E protein are not always lethal although this is virus type dependent. The E protein facilitates assembly and release of the virus (see section on Assembly and Release of

Coronaviruses), but also has other functions. For instance, the ion channel activity in SARS-CoV E protein is not required for viral replication but is required for pathogenesis [30]. The N protein constitutes the only protein present in the nucleocapsid. It is composed of two separate domains, an N-terminal domain (NTD) and a C-terminal domain (CTD), both capable of binding RNA ***in vitro***, but each domain uses different mechanisms to bind RNA. It has been suggested that optimal RNA binding requires contributions from both domains. N protein is also heavily phosphorylated, and phosphorylation has been suggested to trigger a structural change enhancing the affinity for viral versus non-viral RNA. N protein binds the viral genome in a beads-on-a-string type conformation. Two specific RNA substrates have been identified for N protein; the TRSs and the genomic packaging signal. The genomic packaging signal has been found to bind specifically to the second, or C-terminal RNA binding domain. N protein also binds nsp3, a key component of the replicate complex, and the M protein. These protein interactions likely help tether the viral genome to the replicate-transcriptase complex (RTC), and subsequently package the encapsulated genome into viral particles[31-35]. A fifth structural protein, the hemagglutinin-esterase (HE), is present in a subset of β-coronaviruses. The protein acts as a hemagglutinin, binds sialic acids on surface glycoproteins and contains acetyl-esterase activity. These activities are thought to enhance S protein-mediated cell entry and virus spread through the mucosa. Interestingly, HE enhances murine hepatitis virus (MHV) neuro virulence; however, it is selected against in tissue culture for unknown reasons [36-37].

1.5. *Symptoms*[38]

The incubation period is approximately 5 days (range 2-15 days), with 94% of patients showing signs of disease by day 12. Typical presenting symptoms are non specific and include fever, chills, nonproductive cough, dyspnea, rigor, headache, myalgia and malaise. Some patients present with gastrointestinal symptoms, including diarrhea, nausea and vomiting, and abdominal pain. Acute renal impairment is a unique feature of MERS and occurs with significantly greater frequency than was seen in patients with SARS. Symptoms and manifestations of Middle Eastrespiratory syndrome range from mild or a symptomatic infection to severe pneumonia, acute respiratory distress, septic shock and multi organ failure resulting in death. Respiratory failure with ARDS and multiorgan dysfunction syndrome are not uncommon, and the majority of patients with these complications will require admission to the intensive care unit within 2-5 days of symptom onset. The median time from symptom onset to invasive ventilation and/or extra corporeal membrane oxygenation in these patients is 4.5 to 7 days. Risk of severe disease is higher in men over age 45, people with pre existing medical conditions including diabetes, obesity chronic kidney disease, chronic cardiac disease and COPD [39].

1.6. Diagnosis of Covid-19

1.6.1. Blood and sputum cultures

Collect blood and sputum specimens for culture in all patients to rule out other causes of lower respiratory tract infection and sepsis, especially patients with an atypical epidemiological history. Specimens should be collected prior to starting empirical antimicrobials if possible. [40]

1.6.2. Chest X-ray

All imaging procedures should be performed according to local infection prevention and control procedures to prevent transmission. Order a chest X-ray in all patients with suspected pneumonia. Unilateral lung infiltrates are found in 25% of patients, and bilateral lung infiltrates are found in 75% of patients[41, 42].

1.6.3. Computed tomography

Consider ordering a computed tomography (CT) scan of the chest. CT imaging is the primary imaging modality in some countries, such as China. It may be helpful in making the diagnosis, guiding individual patient management decisions, aiding the diagnosis of complications, or giving clues to an alternative diagnosis. However, it is not diagnostic for COVID-19 and local guidance should be consulted on whether to perform a CT scan. The British Society of Thoracic Imaging (BSTI) recommends CT imaging in patients with clinically suspected COVID-19 who are seriously ill if chest x-ray is uncertain or normal. Without the suspicion of COVID-19, the radiology is non-specific and could represent many other disease processes. The BSTI in collaboration with NHS England have produced a radiology decision support tool to help clinicians decide whether or not chest imaging should be ordered [43].

1.6.4. BST: Radiology decision support tool for suspected COVID-19

The American College of Radiology recommends reserving CT for hospitalized, symptomatic patients with specific clinical indications for CT, and emphasizes that a normal chest CT does not mean that a patient does not have COVID-19 and that an abnormal chest CT is not specific for COVID-19 diagnosis. Abnormal chest CT findings have been reported in up to 97% of COVID-19 patients in one meta-analysis of 50,466 hospitalized patients. Evidence of pneumonia on CT may precede a positive RT-PCR result for SARS-CoV-2 in some patients. CT imaging abnormalities may be present in minimally symptomatic or asymptomatic patients [45]. Some patients may present with a normal chest finding despite a positive RT-PCR. Also, results of RT-PCR testing may be false-negative, so patients with typical CT findings should have repeat RT-PCR testing to confirm the diagnosis[44].

1.7. Prevention of Covid-19 **[45, 46, 47]**

1. Clean your hands often, Wash your hands often with soap and water for at least 20 seconds. If soap and water are not available, clean your hands with an alcohol-based hand sanitizer that contains at least 60 to 95% alcohol, covering all surfaces of your hands and rubbing them together until they feel dry. Soap and water is preferred if hands are visibly dirty. Avoid touching your eyes, nose, and mouth with unwashed hands.
2. Avoid sharing personal household items you should not share dishes, drinking glasses, cups, eating utensils, towels, or bedding with other people or pets in your home. After using these items, they should be washed thoroughly with soap and water and dried before use by others.
3. Clean all “high-touch” surfaces every day
   High touch surfaces include counters, tabletops, doorknobs, bathroom fixtures, toilets, phones, keyboards, tablets, and bedside tables. Labels contain instructions for safe and

effective use of the cleaning product including precautions you should take when applying the product, such as wearing gloves and making sure you have good ventilation during use of the product.

4. Practice respiratory hygiene (i.e., cover mouth and nose when coughing or sneezing, discard tissue immediately in a closed bin, and wash hands)
5. Seek medical care early if they have a fever, cough, and difficulty breathing, and share their previous travel and contact history (travelers or suspected/confirmed cases) with their healthcare provider.
6. Stay at home if they are sick, even with mild symptoms, until they recover (except to get medical Care)
7. Clean and disinfect frequently touched surfaces daily (e.g., light switches, door knobs, countertops, handles, phones).
8. The World Health Organization (WHO) does not recommend that people wear a medical mask in community settings if they do not have respiratory symptoms (unless they are caring for someone who is sick) as there is no evidence available on their usefulness to protect people who are not ill.
9. Social distancing

   Many countries have implemented mandatory social distancing measures in order to reduce and delay transmission (e.g., city lockdowns, stay-at-home orders, curfews, non-essential business closures, and bans on gatherings, school and university closures, travel restrictions and bans, remote working, quarantine of exposed people/travelers)

1.8. Treatment of Covid-19 **[48]**

A. **Remdesivir: -** An investigational antiviral drug called remdesivir is being studied in clinical trials in China, the United States, and the United Kingdom.
B. **Lopinavir and Ritonavir: -** a drug combination called lopinavir/ritonavir approved to treat HIV under the brand name Kaletra is being studied in combination with the flu drug Oseltamivir (Tamiflu) in Thailand. **Update**: March 18, 2020 -- According to a study in the **New England Journal of Medicine,** the lopinavir/ritonavir combination showed no benefit over standard care in hospitalized adult patients with severe COVID-19.
C. **Favipiravir: -** An antiviral drug called favipiravir which was reported February 17, 2020 to have received marketing approval in China for the treatment of influenza, was also approved for use in clinical trials as a treatment for novel coronavirus pneumonia.
D. **Fingolimod: -** An approved drug called fingolimod (marketed under the brand name Gilenya for the treatment of relapsing forms of multiple sclerosis) is being studied as a treatment for COVID-19.
E. **Methylprednisolone** is being studied for safety and effectiveness in the treatment of novel coronavirus pneumonia in a number of hospitals.

F. **Chloroquine phosphate: -** The older anti-malaria drug chloroquine has been shown to have a wide range of antiviral effects, including anti-coronavirus. Studies in suggest that chloroquine may help improve patient outcomes in people with novel coronavirus pneumonia.

G. **Hydroxychloroquine sulfate: -** It was reported in the journal **clinical infectious diseases** on March 9 that the malaria drug hydroxychloroquine was effective in killing the coronavirus in laboratory experiments. Hydroxychloroquine was first approved by the FDA in 1995 under the brand name Plaque nil, and it is also used in the treatment of patients with lupus and arthritis.

H. **Bevacizumab: -** A VEGF inhibitor called bevacizumab (marketed under the brand name Avastin for certain types of cancer) being studied as a treatment for acute lung injury (ALI) and acute respiratory distress syndrome (ARDS) in critically ill patients with COVID-19 pneumonia.

I. **Hydroxychloroquine and Azithromycin: -** In a small study commissioned by the French government, 20 patients with COVID-19 were treated with a combination of the anti-malaria drug hydroxychloroquine and the macrolide antibacterial drug azithromycin (Zithromax). Results showed that all patients taking the combination were virologically cured within 6 days of treatment.

J. **Leronlimab: -** A CCR5 antagonist called leronlimab has shown promise in calming the 'cytokine storm' in a small number of critically ill COVID-19 patients hospitalized in the New York area.

K. **Ivermectin: -** An anti-parasitic drug called ivermectin has been shown to be effective against the SARS-CoV-2 virus in an **in-vitro** laboratory study by researchers at Monash University in Melbourne, Australia. Further clinical trials need to be completed to confirm the effectiveness of the drug in humans with COVID-19.

L. **Convalescent Plasma Therapy**

Currently, there are no effective vaccine and specific antiviral medicines are available, convalescent plasma therapy could be an alternative strategy for COVID-19 treatment, especially among severely infected patients.

Convalescent plasma therapy, a classic adaptive immunotherapy, has been used for the prevention and treatment of many infectious diseases for more than one century. Over the past two decades, Convalescent plasma therapy was successfully used in the treatment of SARS, MERS, and 2009 H1N1 pandemic with the satisfactory efficacy and safety.

Evidence shows that convalescent plasma therapy might be a promising treatment option for COVID-19.Convalescent plasma from patients who have recovered from COVID-19 with a high neutralizing antibody titer can be used as a treatment without the occurrence of severe adverse events. Nevertheless, the potential clinical benefit and risk of convalescent blood products in COVID-19 remains uncertain. Therefore, it might be worthwhile to test the safety and efficacy of convalescent plasma transfusion in SARS-CoV-2-infected patients [49-55].

2. CONCLUSION

Despite some diversity in initial symptoms, most COVID-19 patients have fever and respiratory symptoms. For now, travel history to epidemic areas is important to the diagnosis and should be obtained on all patients with flu-like syndromes. If positive, timely referral to the public health authorities for testing is crucial. Frontline medical staffs are at risk and should employ protective measures. Treatment is mainly supportive and symptomatic, though trials of vaccines and antivirals are underway. Healthcare providers should follow subsequent reports as the situation will likely change rapidly.

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