



Review article

What clinicians should know about COVID 19? A review article

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ABSTRACT

Coronavirus Disease 19 (COVID-19) is still raging all over the world causing increased hospitalization, deaths and disrupting social and economic activities. Like any other new disease, the biology and natural history of COVID-19 is not well understood. New information regarding the virus and the disease is frequently evolving leading to quick changes in disease management and preventive methods. A lot of epidemiological and clinical studies are conducted in different parts of the world to generate information that will foster understanding of the disease. But also, there are a lot of misinformation and conspiracy theories surrounding COVID-19 pandemic. Sometimes, clinicians and other health workers are swayed away by false information, ending up giving wrong recommendations to patients and the public. This can be a setback to the efforts in containing the pandemic. This review is intended to provide updated information on the natural history of the disease and available interventions.

Introduction

Severe acute respiratory syndrome corona virus type 2 (SARS-CoV-2) has caused the worst pandemic for the past 100 years. From when it was first reported in Wuhan, China in late December 2019 up to January 2020, this novel coronavirus has spread almost in every country in the world [1]. Within this period, the World Health Organization (WHO) estimated that it had infected around 104 million people globally, overwhelming health systems, putting social lives of many in turmoil, disrupting economies and claiming around 2.3 million lives [1].

Virology

Severe acute respiratory syndrome corona virus type 2 is a beta coronavirus similar to previously reported coronavirus such as SARS and Middle East Respiratory Syndrome coronavirus (MERS) [2,3], which have evolved from animals through antigenic shift and drift and finally becoming able to infect and cause disease in human

[3,4]. The current genetic sequence studies suggest that SARS-CoV-2 has originated from bats and pangolins, but the intermediate host is not well known. However, it is suggested that the live animal markets in China might have potentiated the original transmission of SARS-CoV-2 from these animal reservoirs to human [5–8].

Apart from SARS-CoV-2, MERS and SARS; other serotypes which are infective to human include HCoV-229E, HCoV-NL63, HCoV-HKU1 and HCoV-OC43. However, most of these serotypes are less pathogenic causing only milder disease spectrum.

Severe acute respiratory syndrome corona virus type 2 is a single stranded positive RNA virus with a crown like spiked envelope. It contains four structural proteins; spike protein (S), nucleocapsid protein (N), membrane protein (M), envelope protein (E) and accessory protein hemagglutinin esterase (HE) [9,10]. These structural proteins are

involved in host cell invasion, replication and pathogenesis, as well as antigenic properties [11,12].

The S protein which forms the characteristic crown-like appearance is responsible for binding on receptors of the host cell membranes, thus facilitating attachment and entry into the host cell. The M protein extends on the external surface and it has been implicated in virus assembly while the envelope protein (E) is involved in virus assembly and release [12]. The nucleocapsid protein N forms the viral nucleocapsid. Its function is not well known, but it has been associated with viral RNA synthesis and viral budding [12,13]. Hemagglutinin esterase protein (HE) is also involved in viral binding on the receptor and adsorption into the host membrane [14].

Transmission

Respiratory droplets and contaminated surfaces are the main source of transmission. The chances of infection from droplets is high when the infected person with or without symptoms coughs, sneezes or speaks loudly within a distance of 1 meter producing virus loaded oral or nasal droplets. Someone is at higher risk of getting infected if these potentially infective droplets get access to the mucous membranes in the mouth, nose, and eyes [15,16].

Intensive care unit procedures for infected patients such endotracheal intubation, may increase the risk of transmission of SARS-COV-2 among health care personnel in hospital setting [17]. Also, the risk is high in poorly ventilated and highly populated areas such as public transport (buses and trains), and indoor gatherings.

Transmission also occurs through accidentally touching your mouth, nose or eyes, after contact with fomites directly from infected person or from the surfaces and objects such as furniture, doors, toys etc [18–20]. The persistence of the virus on these surfaces depend on several factors such as nature of the surfaces (materials), temperature, humidity, and sunlight. The virus can be effectively inactivated on surfaces using disinfectants such as 60-71% ethanol, 0.5% hydrogen peroxide or 0.1% sodium hypochlorite [21].

There is no evidence of developing COVID-19 by fecal oral transmission, but detection of the virus in the stool of infected patients suggests the possibility of transmission through stool contaminated materials [22–24].

Once the SARS-Cov-2 have accessed the mucous membranes, follows a well-coordinated process involving attachment to receptors, penetration, biosynthesis, maturation and release of mature virus ready for invading other cells. The S-glycoprotein which is present on the surface of coronavirus, attach to host cells via angiotensin converting enzymes type 2 (ACE-2) as the receptor molecule which is highly expressed in lungs (epithelial cells and type 1 pneumocytes), heart, esophagus, ileum, urine bladder, and the kidney [25–27].

After attachment, several viral proteases enzymes are activated facilitating the entry of virus in the host cells [28,29]. In the cytoplasmic membranes of the host cells, the viral genome is transcribed producing multiple copies of viral RNA. This complex process is highly facilitated by RNA dependent RNA polymerase and other replicase-transcriptase proteins, leading to synthesis of several RNA copies from the original template [27–31].

Several polyproteins are also synthesized during the process and later cleaved by viral encoded proteinases and assembled into a membrane bound translation-transcription complex (RTC), which later, form double membrane virion containing vesicles which fuse with the plasma membrane of the host cell releasing the virus ready to attack other cells [31].

Pathophysiology

The invasion and rupture of host cells such as pneumocytes 2 by the virus, initiates the cascade of immunological response which are responsible for the clinical picture of COVID-19. Dendritic cells and macrophages form the first line innate immune response by scavenging on the infected cells. These are also antigen presenting cells; they present viral antigen to other defensive T cells (CD 4 and CD8). CD8 are natural killer cells; they kill the virus while CD4 activates the B cells to produce SARS-COV-2 specific antibodies [9,32].

These cascade of events, lead to production of pro-inflammatory cytokines such as interleukins (IL-6 and 10), granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory proteins (MIP1 α) and tissue necrosis factor (TNF)- α which potentiates further inflammatory storm, leading to lung tissue inflammation and reduced function [32]. These changes include oedema, proteinaceous exudate filled alveoli, vascular congestion and

inflammatory clusters with fibrinous materials, leading to reduced lung compliance, and eventually severe acute respiratory syndrome [33,34].

Other systemic response of cytokine storm includes activation of alternative complement pathway leading to vasculopathy, coagulation activation, endothelial dysfunction, and multiorgan failure [35–41]. Severe acute respiratory syndrome corona virus type 2 has been found to directly invade endothelial cells in multiple organs through ACE 2 receptors leading to recruitment of inflammatory cells through the above mentioned mechanism leading to vascular endothelial inflammation (endothelitis), tissue oedema, ischemia and cell death [42]. Hence, inadequate gas exchange due to lung pathology, thromboembolism, and vasculopathy leads to ischemia, hypoxemia, acidosis, and consequently, multiorgan failure.

Clinical presentation

COVID-19 has a wide spectrum of presentation, ranging from asymptomatic or mild symptoms (80.9%) to severe life-threatening presentation (14%). Patients with co-morbidities such as cancer, cardiovascular diseases, asthma, diabetes, hypertension, immunodeficiency states and the elderly above 60 years are at higher risk of developing more severe clinical features and increased fatality [43].

It usually takes an average of five days from initial exposure of the virus to development of symptoms [15,44]. For symptomatic patients, most common clinical presentations include fever (83-99%), cough (69-82%), fatigue (44-70%), anorexia (40-88%), difficulty in breathing (31-40%) and myalgia (11-35%). Other symptoms include nausea, loss of taste, vomiting, and diarrhea. Features may progress to respiratory failure, multiorgan dysfunction, and death [35,38,43].

World Health Organization has classified COVID-19 severity as mild, moderate or severe depending on signs, symptoms and investigational results. A mild disease is defined as a symptomatic patient meeting the case definition of COVID-19 without evidence of viral pneumonia or hypoxia [45].

Moderate disease comprises of Adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) but no signs of severe pneumonia, including $SpO_2 \geq 90\%$ on room air (54). Child with clinical signs of non-severe pneumonia (cough or difficulty breathing + fast

breathing and/or chest in drawing) and no signs of severe pneumonia (Fast breathing (in breaths/min): < 2 months: ≥ 60 ; 2–11 months: ≥ 50 ; 1–5 years: ≥ 40) [45].

Severe disease is defined as adolescent or adult with clinical signs of pneumonia (fever, cough, dyspnoea, fast breathing) plus one of the following: respiratory rate > 30 breaths/min; severe respiratory distress; or $SpO_2 < 90\%$ on room air. Child with clinical signs of pneumonia (cough or difficulty in breathing) AND at least one of the following: Central cyanosis or $SpO_2 < 90\%$; severe respiratory distress (e.g. fast breathing, grunting, very severe chest in drawing); general danger signs: inability to breastfeed or drink, lethargy or unconsciousness, or convulsions (55,56). Fast breathing (in breaths/min): < 2 months: ≥ 60 ; 2–11 months: ≥ 50 ; 1–5 years: ≥ 40 . While the diagnosis can be made on clinical grounds; chest imaging (radiograph, CT scan, ultrasound) may assist in diagnosis and identify or exclude pulmonary complications.

Diagnosis and laboratory findings

A confirmatory test is performed When COVID 19 is suspected based on clinical presentation and exposure history. WHO defines a suspect case as a patient with acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath), AND a history of travel to or residence in a location reporting community transmission of COVID-19 disease during the 14 days prior to symptom onset; OR A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case ;OR A patient with severe acute respiratory illness (fever and at least one sign/symptom of respiratory disease, e.g., cough, shortness of breath; AND requiring hospitalization) AND in the absence of an alternative diagnosis that fully explains the clinical presentation in the last 14 days prior to symptom onset [46].

The best specimen is the oral pharyngeal or nasopharyngeal swab; however, sputum and endotracheal aspirates or bronchoalveolar lavage can also be used. Currently, the gold standard test is real time polymerase chain reaction (RT-PCR) aimed at detecting viral RNA in the study specimen [47,48]. Other immunodiagnostic tests (antigen and antibody based point of care rapid tests) have been developed, but their reliability is questionable due to wide range of sensitivity and specificity and potential cross reaction with other human coronaviruses [49,50]. They have been recommended by WHO for

use in research setting but not for diagnosis or clinical decision making.

The most common hematological changes observed in complete blood count (CBC) include leucopenia with profound lymphopenia which correlates with disease severity. Thrombocytopenia is not a common finding compared to other severe viral illnesses [51–53]. Also, other inflammatory markers such as CRP, ESR, and serum ferritin are significantly elevated in severely ill patients [51,54] as well as markers of increased disseminated intravascular coagulopathy (DIC) such as D-dimers and fibrin/fibrinogen degradation products (FDP) [39,55]. Some studies have demonstrated that; lymphopenia, elevated CRP, increased LDH as well as increased interleukin-6 are highly associated with disease severity and chances of death. These parameters may be used for guidance in clinical decisions such as managing the patient in the ICU or for monitoring the clinical progression of the patient [51,54].

Radiological imaging findings in chest x-ray are not specific for covid-19 but are similar to other atypical or organizing pneumonias. These findings include peripheral ground-glass opacities in both lungs, while crazy paving appearance and consolidation are the most common findings in the chest CT scan [56].

Treatment

The mainstay treatment is conservative for asymptomatic and mild cases with main focus on relieving symptoms such as fever by using antipyretics and hydration. Supplemental oxygen should be considered in patients with SpO₂ < 90% or/and other emergency signs such as obstructed or absent breathing, severe respiratory distress, central cyanosis, shock, coma and/or convulsions [57]. When oxygen therapy using mask or nasal prongs is not enough to maintain SpO₂ above 90%, endotracheal intubation should be considered in prone position to ensure adequate oxygenation [58].

Coagulation studies such as D-dimers and prothrombin time, should be monitored closely in patient with severe disease. In case of evidence of DIC, patients may be put on prophylactic dose of anticoagulation such as Low Molecular Weight Heparin (LMWH) to prevent further escalation of coagulopathy [59–61].

Preliminary results from a clinical trial in United Kingdom (in press), has shown that the use of dexamethasone, a steroidal anti-inflammatory

drug can be a lifesaving especially in critically ill patients. It has been shown that, it reduces mortality in one third of patients on ventilators and one fifth of the patients requiring oxygen therapy.

Use of antibiotics can only be considered in case of evidence of superimposed bacterial infection, but routine prophylactic use is discouraged as may increase the chance of antimicrobial resistance [62].

Prevention

Prevention is crucial for SARS-CoV-2 control, keeping in mind that there is no specific effective treatment and vaccine. Frequent hand hygiene by washing hands with running water and soap at least for 20 seconds has proved to eliminate the virus on hands which might have been obtained from infected people, contaminated surfaces, and objects [63,64]. Regular washing prevents infection (through touching the eyes, nose and mouth), and spreading the virus to other objects and surfaces. When water is not readily available, alcohol based hand sanitizer which contains at least 60% alcohol can be used [20].

It is advised to wear face mask especially when in public places during COVID-19 epidemics. When well used, community-wide wearing of mask have been proved to significantly reduce community transmission of COVID-19 [65]. The face mask prevents the inhalation of the virus containing respiratory droplets emitted from infected person by coughing or sneezing. When in public place and no face mask, coughs and sneezes should be covered using a tissue or the inside of the elbow. The tissue should be disposed in the trash and hand washed by running water and soap or use hand sanitizer if available.

Non-medical masks made of common fabrics such as cotton can be used by healthy individuals in the community to prevent infection from asymptomatic individuals, but medical masks are recommended for infected individuals or those who are taking care of the infected individuals. Also, WHO recommend the use of N95 facemask or respirators to be prioritized to health care workers who are working in high COVID -19 risk areas [66].

During COVID-19 outbreak, the most frequently touched surfaces and objects in public places such as door knobs, handles, tables etc., should be disinfected frequently by using household disinfectants [67].

Social distancing e.g. avoiding gathering and keeping distance at least 2 meters in public places is advised during COVID-19 outbreak. This is usually done in parallel with disease containment measures such as contact tracing, testing and quarantining those who have been in contact with confirmed cases. For effective disease control, these measures should not be taken in isolation; combined interventions are more effective than a single measure.

Several vaccines have been found to be safe, and able to prevent development of clinical disease by 75-95% among vaccinated individuals [68–70]. However, there is data gap on the efficacy of the vaccine in children. It is also not yet known if the vaccine can prevent someone from being infected or from transmitting the virus to another person who is not vaccinated.

Due to paucity of effective drug and vaccine, most of the focus should be on prevention of the disease by hand hygiene, using of face mask, social distancing as well escalated community testing, isolation of the infected individuals as well as quarantining those who have been in contact with confirmed cases. Infection prevention and control (IPC) measure should be over emphasized especially in health care facilities and public places. Patient's clinical presentation and routine investigation findings should guide clinician on making decisions on patient's management.

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