COVID-19

The COVID-19 pandemic is perhaps the greatest healthcare challenge of a generation. It is a new pathogen that is highly contagious, can spread quickly, and must be considered capable of causing enormous health, economic and societal impacts in any setting. COVID-19 is caused by the most recently discovered coronavirus. This new virus and the disease were unknown before the outbreak began in Wuhan, China, in December 2019. COVID-19 has now affected several countries and has caused widespread death.

Coronaviruses are a large family of viruses which may cause illness in animals or humans. In humans, several coronaviruses are known to cause respiratory infections ranging from the common cold to more severe diseases such as Middle East Respiratory Syndrome (MERS) and Severe Acute Respiratory Syndrome (SARS). The most recently discovered coronavirus causes coronavirus disease COVID-19.

Epidemiology

Symptomatic patients can transmit infection through large droplets generated during coughing and sneezing. The disease can also be contracted from asymptomatic people and before the onset of any symptom. These infected droplets can spread 1–2 metres and deposit on different surfaces. Infection is acquired either by inhalation of these droplets or touching areas contaminated by them and then touching the nose, mouth and eyes.

The virus can remain viable on surfaces for days in favourable atmospheric conditions but are destroyed in less than a minute by common disinfectants like sodium hypochlorite, hydrogen peroxide etc. Higher viral loads is seen in the nasal cavity as compared to the throat and studies have shown no difference in viral burden between symptomatic and asymptomatic people.

Pathogenesis

Although much is known about the mortality of this clinical disease, much less is known about its pathobiology. A probable course of events can be postulated based on past studies with SARS-CoV. Cellular biology is useful for framing research questions and explaining the clinical course by focusing on the areas of the respiratory tract that are involved. Based on the cells that are likely infected, COVID-19 can be divided into three phases that correspond to different clinical stages of the disease.

Stage 1 | **Asymptomatic state** (initial 1–2 days of infection)

The inhaled virus SARS-CoV-2 likely binds to epithelial cells in the nasal cavity and starts replicating. ACE2 is the main receptor for both SARS-CoV-2 and SARS-CoV. In vitro data with SARS-CoV indicate that the ciliated cells are primary cells infected in the conducting airways There is local propagation of the virus but a limited innate immune response. At this stage the virus can be detected by nasal swabs. Although the viral burden may be low, these individuals are infectious. The RT-PCR value for the viral RNA might be useful to predict the viral load and the subsequent infectivity and clinical course. Perhaps super spreaders could be detected by these studies. For the RT-PCR cycle number to be useful, the sample collection procedure would have to be standardised. Nasal swabs might be more sensitive than throat swabs.

Stage 2 | **Upper airway and conducting airway response** (next few days)

The virus propagates and migrates down the respiratory tract along the conducting airways, and a more robust innate immune response is triggered. Nasal swabs or sputum should yield the virus (SARS-CoV-2) as well as early markers of the innate immune response. At this time, the disease COVID-19 manifests clinically. The level of CXCL10 (or some other innate response cytokine) may be predictive of the subsequent clinical course. CXCL10 is an interferon responsive gene that has an excellent signal to noise ratio in the alveolar type II cell response to both SARS-CoV and influenza. CXCL10 has also been reported to be useful as disease marker in SARS. Determining the host innate immune response might improve predictions on the subsequent course of the disease and need for more aggressive monitoring.

For about 80% of the infected patients, the disease will be mild and mostly restricted to the upper and conducting airways. These individuals may be monitored at home with conservative symptomatic therapy.

Stage 3 | **Hypoxia, ground glass infiltrates, and progression to ARDS**

Unfortunately, about 20% of the infected patients will progress to stage 3 disease and will develop pulmonary infiltrates and some of these will develop very severe disease. Initial estimates of the fatality rate are around 2%, but this varies markedly with age. The virus now reaches the gas exchange units of the lung and infects alveolar type II cells. Both SARS-CoV and influenza preferentially infect type II cells compared to type I cells. SARS-CoV propagates within type II cells, large number of viral particles are released, and the cells undergo apoptosis and die. The end result is likely a self-replicating pulmonary toxin as the released viral particles infect type II cells in adjacent units. The pathological result of SARS and COVID-19 is diffuse alveolar damage with fibrin rich hyaline membranes and a few multinucleated giant cells. The aberrant wound healing may lead to more severe scarring and fibrosis than other forms of Acute Respiratory Distress Syndrome (ARDS). Recovery will require a vigorous innate and acquired immune response and epithelial regeneration. Elderly individuals are particularly at risk because of their diminished immune response and reduced ability to repair the damaged epithelium. The elderly also have reduced mucociliary clearance, and this may allow the virus to spread to the gas exchange units of the lung more readily.

There are significant knowledge gaps in the pathogenesis of COVID-19. If it is confined to the conducting airways, it should be mild and treated symptomatically at home. However, COVID-19 that has progressed to the gas exchange units of the lung must be monitored carefully and supported to the best of our ability.

Clinical Presentation

The signs, symptoms, disease progression and severity:

Symptoms of COVID-19 are non-specific and the disease presentation can range from no symptoms (asymptomatic) to severe pneumonia leading to death. As of 20 February, 2020 and based on 55,924 laboratory confirmed cases – data as released in the Report of the WHO-China Joint Mission on Coronavirus Disease 2019 (COVID-19) – typical signs and symptoms include: fever (87.9%), dry cough (67.7%), fatigue (38.1%), sputum production (33.4%), shortness of breath (18.6%), sore throat (13.9%), headache (13.6%), myalgia or arthralgia (14.8%), chills(11.4%), nausea or vomiting (5.0%), nasal congestion (4.8%), diarrhea (3.7%), and hemoptysis (0.9%), and conjunctival congestion (0.8%).

Most people infected with COVID-19 virus experience mild disease and recover. Approximately 80% of laboratory confirmed patients have had mild to moderate disease, which includes non-pneumonia and pneumonia cases, 13.8% have severe disease (dyspnea, respiratory frequency ≥30/minute, blood oxygen saturation ≤93%, PaO2/FiO2 ratio <300, and/or lung infiltrates >50% of the lung field within 24-48 hours) and 6.1% are critical (respiratory failure, septic shock, and/or multiple organ dysfunction/failure).

Risk Factors

Individuals at highest risk for severe disease and death include people aged over 60 years and also those with underlying conditions such as hypertension, diabetes, cardiovascular disease, chronic respiratory disease (COPD, Asthma & Pulmonary TB) and cancer.

Diagnostic Approach

A suspect case is defined as one with fever, sore throat and cough who has history of travel or contact with patients with similar travel history or those with confirmed COVID-19 infection.

Specific diagnosis is by specific molecular tests on respiratory samples (throat swab/ nasopharyngeal swab/sputum/endotracheal aspirates and Broncho alveolar lavage).

Routine laboratory investigations are usually nonspecific. WBC 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.

Radio diagnostic chest radiography is often the first diagnostic test performed for respiratory diseases but may be normal in early disease. It usually shows bilateral infiltrates.

The CT chest imaging is more sensitive and specific and generally shows infiltrates, ground glass opacities and sub segmental consolidation. It is also abnormal in asymptomatic patients. 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.

Differential Diagnosis

The differential diagnosis includes all types of respiratory viral infections [influenza, parainfluenza, respiratory syncytial virus (RSV), adenovirus, non COVID-19 coronavirus], atypical organisms (mycoplasma, chlamydia) and bacterial infections. It is not possible to differentiate COVID-19 from these infections clinically or through routine lab tests.

Management

Treatment is essentially supportive and symptomatic.

The first step is to ensure adequate isolation to prevent transmission to other contacts, patients and healthcare workers. Mild illness can be managed at home with counseling about danger signs. Routine use of antibiotics and antivirals 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. The role of corticosteroids is unproven; while current international consensus and World Health Organization (WHO) advocate against their use.

Prevention

Prevention is crucial. Hand hygiene and use of face mask, hand gloves, personal distancing and avoiding crowd are the need of the hour. However, several properties of this virus make prevention difficult namely, non-specific features of the disease, the infectivity even before onset of symptoms in the incubation period, transmission from asymptomatic people, long incubation period, tropism for mucosal surfaces such as the conjunctiva, prolonged duration of the illness and transmission even after clinical recovery.