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Original Research Paper

Medicine

SARS-CoV-2

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KEYWORDS :

OVERVIEW

The Novel Coronavirus (SARS-CoV-2) was first identified by health authorities in Wuhan, China in December 2019 as rates of pneumonia of unknown aetiology began to rise. In February 2020, the disease caused by SARS CoV-2 virus was labelled Coronavirus Disease of 2019 (COVID-19) by the World Health Organisation (WHO). Within weeks, the disease had rapidly spread across the world resulting in WHO declaring COVID-19 a pandemic on the 11th of March 2020.

Coronaviruses are non-segmented enveloped positive-sense RNA viruses common in humans as well as animals and belonging to the family Coronaviridae. In addition to SARS CoV-2 Novel Coronavirus, there are six other strains of coronavirus, including 229E and NL63 (Alpha Coronavirus), OC43, HKU1, MERS-CoV and SARS-CoV (Beta Coronavirus).

EPIDEMIOLOGY

COVID-19 can infect individuals of all ages; however, middle aged and elderly individuals appear to be more at risk of suffering moderate to severe infections. Children typically suffer mild infections with fewer complications. The disease appears to affect both males and females equally. SARS-CoV-2 has an incubation period typically ranging from 2-14 days, with the median incubation period being 5-6 days. It is estimated that the case fatality rate is 2-4%.

Ro (pronounced "R naught") is an epidemiological term also known as the 'reproduction number'. It is used to indicate how contagious an infectious disease is by describing how many cases on average a single infected patient will go on to cause. The Ro value for SARS CoV-2 is estimated to be between 3-4.

MODES OF TRANSMISSION

The predominant mode of transmission is via respiratory droplets, typically generated from symptomatic patients by coughing or sneezing. These droplets containing virus particles enter the body through the eyes, nose or mouth and once in contact with the mucosal membranes, are able to begin replicating, thus infecting the new host. Similarly, touching an area or object that has virus particles on its surface and then subsequently touching the eyes, nose or mouth can also cause infection.

It is believed that respiratory droplets (defined as droplets >5-10 μm) are unable to travel further than one metre. Patients appear to be most contagious when they are symptomatic (i.e. coughing and sneezing, thus releasing contaminated droplets); however, it is believed that asymptomatic transmission is possible. Airborne transmission differs from droplet transmission in that the particles are smaller (<5 μm) and therefore able to travel further and remain suspended in the air for longer. With regards to COVID-19 specifically, airborne transmission may be possible in aerosol-generating procedures such as endotracheal intubation, bronchoscopy, etc. and in such cases it is believed that the aerosolised droplets can remain suspended in the air for up to three hours. There have also been isolated cases of potential vertical transmission from mother to newborn but it is unclear if the virus was transmitted in the womb or after birth and hence, more evidence is required.

CASE DEFINITIONS

According to the WHO case definitions.

Suspected Case:

A. 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

B. A patient with any acute respiratory illness AND having been in contact with a confirmed or probable COVID-19 case (see definition of contact) in the last 14 days prior to symptom onset; OR

C. 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.

Probable Case:

A. A suspect case for whom testing for the COVID-19 virus is inconclusive; OR

B. A suspect case for whom testing could not be performed for any reason.

Confirmed Case:

A person with laboratory confirmation of COVID-19 infection, irrespective of clinical signs and symptoms.

Contact:

A contact is a person who experienced any one of the following exposures during the 2 days before and the 14 days after the onset of symptoms of a probable or confirmed case:

1. Face-to-face contact with a probable or confirmed case within 1 meter and for more than 15 minutes;

2. Direct physical contact with a probable or confirmed case;

3. Direct care for a patient with probable or confirmed COVID-19 disease without using proper personal protective equipment;OR

4. Other situations as indicated by local risk assessments.

MORTALITY

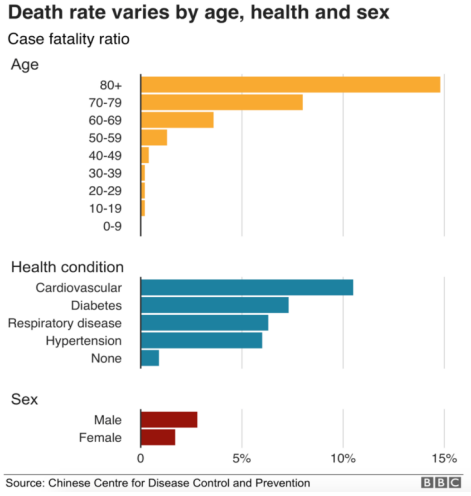

Figure 1: Death Rate by Age, Health & Sex [11]

There have been a number of parameters that are considered to be strong predictors of mortality in patients with COVID-19. These include age over 65, comorbid cardiovascular disease, diabetes, underlying respiratory disease, cerebrovascular disease and hypertension. Other parameters that are commonly used to assess a patient's risk include white cell count, cardiac troponin level and D-Dimer level on admission. It is estimated that of patients aged over 80 years, the death rate in confirmed COVID-19 cases is around 20%. This is compared to a total death rate of approximately 8% in those aged 70-79 years but just 0.2% for those aged under 40 years. ,12 In terms of comorbidities, cardiovascular disease has a mortality rate of approximately 13.2% in confirmed COVID-19 cases and diabetes a mortality rate of approximately 9.2%. These appear to be the most significant comorbid conditions impacting patient outcomes.

Responding to the Threat

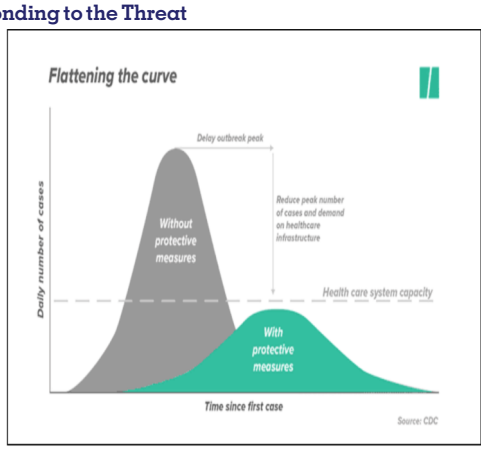

Figure 2: Flattening the Curve [13]

Under normal circumstances, healthcare systems around the world are working at near full capacity, so a relative increase in the number of patients due to the COVID-19 pandemic is undoubtedly overwhelming. Two overarching strategies to tackle this include - raising the capacity of the healthcare system and flattening the curve resulting in a decrease in the total number of sick individuals at a given time. The former is achieved by increasing the number of health professionals and distributing them to areas of high demand, accumulating necessary equipment such as personal protective equipment (PPE), ventilators and mobilising the funds in order to achieve such outcomes. The latter is achieved by slowing the rate of transmission and does not ultimately change the area under the curve, rather it results in the case load being distributed over a longer time period and avoiding a large peak. Slowing the rate of transmission has been successfully achieved in many countries around the world through the implementation of restrictions on public gatherings, travel, etc.

STRUCTURE OF SARS CoV-2

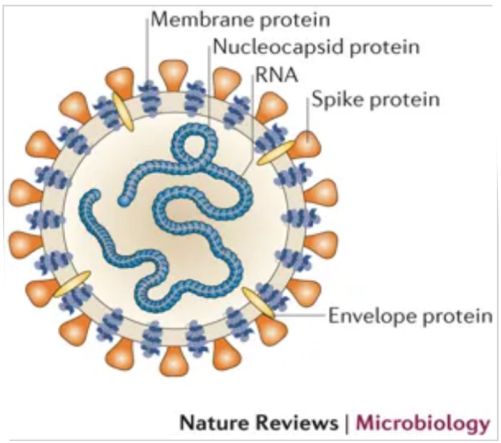

Figure 3: Virus Structure [17]

Since the emergence of SARS CoV-2 in December 2019, it has been identified that the disease belongs to the Beta Coronavirus family. The genome is considered to be almost identical (approximately 96%) to that of bat Coronavirus, thus identifying bats the natural host of the disease., The initial cases of COVID-19 in patients in Wuhan, China were each able to be directly linked to exposure to the Huanan Seafood Wholesale Market of Wuhan. Further research has discovered that the virus attaches to the Angiotensin-Converting Enzyme 2 (ACE2) receptor, using the same mechanism through which SARS-CoV, discovered in 2002, was able to infect patients.

The term Coronavirus stems from the Latin term Coronam meaning crown. This is a reference to the structure of the viral particles which, when viewed under a microscope, show a series of glycoprotein spikes on the viral envelope that resemble a crown.17 The SARS CoV-2 virus membrane consists of four structural proteins including spikes (S), the envelope (E), the viral membrane (M) and the nucleocapsid (N)., 18

The S-protein allows the virus to attach to the ACE-2 receptors on the membrane of host cells. The virus has an affinity for ACE-2 receptors that is 20 times greater than that of SARS CoV, hence the reason for its rapid and extensive spread.16 The S-protein has two functional subunits termed S1 and S2. S1 binds to the host cell receptor and S2 mediates the fusion of the viral and cellular membranes. This protein is of particular interest for future vaccine development and treatment for COVID-19 as it is primarily responsible for inducing the neutralisation of antibodies. The M Protein is the most abundant on the virus' surface, spanning the virus membrane. Its role is predominantly to form virus particles intracellularly that are devoid of the protein S.18 The E Protein plays a critical role in the pathogenicity of SARS CoV-2, being predominantly responsible for assembly and release of the viral particles.18 Its fatty layer disintegrates when it comes into contact with soap, thus making handwashing a critical transmission reduction strategy. Finally, the N Protein binds the virus single stranded RNA and also exhibits host cell defence mechanisms.

PATHOGENESIS

Mechanism of Infection

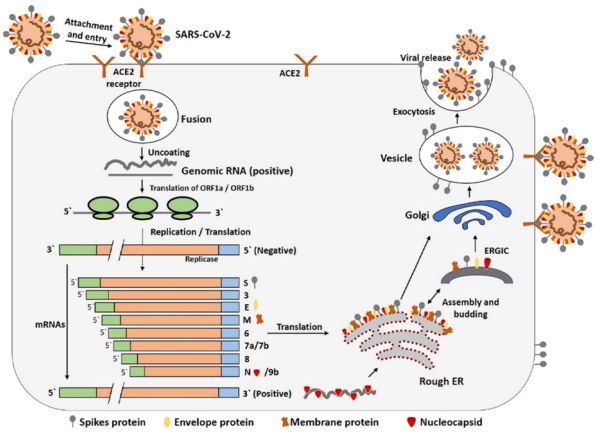

Figure 4 Mechanism of Infection [7]

The process of infection begins with the SARS CoV-2 viral particle invading the host cell. This process begins when the S-Protein on the surface of the viral particle attaches to the cellular ACE-2 receptor.7 The viral envelope then fuses with the cell membrane and the particle is endocytosed. Following its entry, viral RNA is released into the cell and is then translated and cleaved by viral proteinases.7 RNA transcription then occurs and finally the relevant viral structural proteins are produced. The proteins then pass through the Endoplasmic Reticulum and Golgi where they are assembled into virions.7, 19 The virions are packaged into vesicles that are finally released from the cell via exocytosis.

Both SARS CoV and SARS CoV-2 require ACE2 receptors for viral entry and replication, extensive research has proven on animal models that the more ACE2 receptors expressed in a host, the more severe the disease. The lungs are believed to be the most vulnerable target organ as a result of their extensive surface area as well as the high proportion of ACE2 receptor-expressing cells.

Cytokine Storm

The symptoms of critically ill COVID-19 patients are believed to be associated with a cytokine storm. Although the majority of cytokines produced by a SARS-CoV-2 infection are essential in the inflammatory response, they appear to also be counterproductive by inducing cell injury and negatively affecting antibody production by reducing lymphocyte counts. It was found that an increase in inflammatory cytokines such as TNF- , IL-1, IL-6, IL-8 and chemokines caused a further recruitment of inflammatory cells such as neutrophils and monocytes and increased acute phase reactants. The cell injury is believed to result in fibrin deposition and the formation of scar tissue causing lung fibrosis and ultimately hypoxaemia. Furthermore, TNF- and IL-1 specifically have been implemented in causing an increase in vascular permeability, causing interstitial and pulmonary oedema, and thus further reducing oxygen transfer. It is this severe immune response that progressively damages the lung and is the main cause of acute respiratory distress syndrome (ARDS) and multi-organ failure in COVID-19 patients.

CLINICAL PICTURE

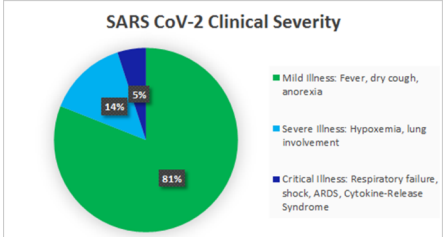

Figure 5: SARS CoV-2 Clinical Severity

The clinical severity of COVID-19 ranges from asymptomatic forms to clinical conditions characterised by respiratory failure and/or multiorgan and systemic manifestations. Patients with COVID-19 typically present with a respiratory syndrome with the majority of presentations being a mild illness. Severe and critical symptoms are more likely to occur in the elderly or the immunocompromised.[5]

Symptoms of a mild illness occurred in 81% of cases and included fever, dry cough, fatigue, dyspnoea and myalgia. The most common symptoms at the onset of illness were fever (seen in 88% of patients) and a dry cough (seen in 67% of patients). Severe disease occurred in 14% of cases where patients typically presented with tachypnoea, SPO2 <93%, PaO2/FiO2 ratio <300, and/or lung infiltrates covering >50% of the lung field. Critical disease such as respiratory failure, shock and multi-organ involvement was only reported in 5% of cases. Less than 1% of all cases were asymptomatic.[5]

INVESTIGATIONS

Laboratory Findings

Upper respiratory tract samples performed via collection of nasopharyngeal and oropharyngeal swabs for Reverse Transcription-PCR (RT-PCR) are being routinely used for COVID-19 testing. This test is able to detect SARS CoV-2 RNA with results taking anywhere between several hours to two days to become available. A positive result should be confirmed by the collection of a second upper respiratory tract sample for an RT-PCR assay which targets an alternative SARS CoV-2 gene. Similarly, should a patient with a high clinical suspicion for COVID-19 have an initial negative result, it is currently recommended by the WHO to re-sample the patient.

Coronavirus testing positivity rates[25]

	Type of specimen	Positive %
1	Bronchoalveolar lavage fluid	93%
2	Sputum	72%
3	Nasal swabs	63%
4	Fibrobronchoscope brush biopsy	46%
5	Pharyngeal swabs	32%
6	Faeces	29%
7	Blood	1%
8	Urine	0%

White blood cell counts have varied significantly amongst patients presenting with COVID-19. Leukocytosis, leukopenia and a mild thrombocytopenia have all commonly been recorded, however the most consistent parameter, present in over 80% of patients on presentation, has been lymphocytopenia. Additionally, whilst non-specific, it has been found that the majority of patients with COVID-19 will have raised C-Reactive Protein (CRP) levels, a marker which has been reliable for tracking disease progression or improvement. Furthermore, elevated initial LDH levels have been detected in many patients requiring intensive care, thus deeming it a poor prognostic factor. Similarly, serum Procalcitonin is often reported as normal in patients with mild to moderate COVID-19, however has been termed a reliable marker of increasing severity of the disease should it become elevated. Less commonly, patients are exhibiting elevated Creatinine Kinase levels, positive D-Dimer tests and deranged liver function including raised alanine aminotransferase (ALT), aspartate aminotransferase (AST) and bilirubin.

Radiological Findings

Chest x-rays have proven to have little benefit in diagnosing COVID-19 as findings are often absent or non-specific. Should changes be apparent, they most commonly consist of bilateral or localised patchy shadowing, ground glass opacification and occasionally interstitial abnormalities.27

Chest CT provides a more comprehensive assessment of the patient's pulmonary condition. Specific changes that have commonly presented in COVID-19 patients include ground glass opacities which are typically subpleural with a lower lobe predominance and as the course of the disease progresses, are often seen bilaterally. Other CT findings include dense pulmonary consolidation and the formation of a 'crazy-paving' pattern.

Rapid Detection Tests

To date, there has been little conclusive evidence surrounding the use of rapid tests for COVID-19 and as a result the World Health Organisation are only endorsing their use for research purposes. These tests are designed to detect IgM and IgG antibodies to SARS CoV-2 in blood, serum and plasma, however evidence suggests that their sensitivity may vary anywhere from 34-80%. Therefore, further research is required prior to these rapid tests being widely available for diagnostic purposes.

MANAGEMENT

Initial Management

Currently, the management of COVID-19 is largely supportive and there is no proven efficacy of any drug for humans as of April 8, 2020. Patients who have mild symptoms can be managed at home if they are educated about the condition, capable of self-monitoring and know how to escalate any concerns. The safe management of these mildly symptomatic patients helps reduce the burden on the hospital system. Patients who have homes not suitable for adequate care should have alternate accommodation arranged or be admitted into the hospital.

Current Proposed Treatments for COVID-19

Treatment	Mechanism	Common Adverse Effects
Chloroquine/ Hydroxychloroquine	Inhibits viral entry by altering pH of endosomes and inhibiting glycosylation of host receptors. Also plays role in reducing cytokine production.	Abdominal cramps, nausea, vomiting, anorexia, diarrhea.[32]
Lopinavir/Ritonavir	Inhibits protease activity and thus blocks cellular entry.[33]	Gastrointestinal upset, nausea, vomiting, diarrhea.[32]
Remdesivir [30, 31]	Inhibits RNA polymerase and prevents viral application.[32, 33] Effective for both prophylaxis and therapy of HCoVs infections	Reversible elevation of transaminases and renal injury.[32]
Umifenovir[32]	Inhibits fusion of S-protein to ACE2 receptor, thus not allowing viral entry to host cell.[32, 33]	Gastrointestinal upset, allergic reaction and elevation of transaminases.[32]
Tocilizumab	Monoclonal antibody that functions by reducing the severity of the cytokine storm via inhibition of Interleukin-6.[32, 33]	Hypertension, infusion-related reaction, increased risk of upper respiratory tract infections, headache and elevated AST.[32]
Convalescent plasma or serum[36]	Contains SARS CoV-2 neutralizing antibodies.[36]	Fever, allergic transfusion reactions, transfusion-associated circulatory overload and transfusion-related acute lung injury.
Intravenous Immunoglobulin	Inhibiting pro-inflammatory cytokines, enhancing regulatory T-Cells and neutralising pathogenic autoantibodies.	Infusion-site reaction, flu-like symptoms, headache, nausea and above-mentioned transfusion-related side-effects.
Zinc	Inhibiting CoV RNA polymerase activity and hampers replication of cells in culture experiments through its antiviral effects.	Nausea, vomiting, diarrhoea, metallic taste.[39]
Ivermectin	Mechanism against Sars-CoV-2 is largely unknown but thought to inhibit the import of nuclear viral proteins and hence control viral replication. A 5000-fold reduction in viral load has been seen in a 48 hour period in a recent study from Monash University.	Fatigue, nausea, vomiting, diarrhoea.

Management of Severe Disease

COVID-19 is associated with severe disease that requires intensive care in approximately 5% of proven infections. Single rooms or negative pressure rooms and contact, droplet and airborne precautions are in place should COVID-19 patients require respiratory support in the form of high-flow nasal oxygen (HFNO), non-invasive ventilation (NIV) or intubation.[41]

In high-flow oxygen therapy, oxygen is delivered in conjunction with compressed air and humidification. It delivers high flow oxygen that is humidified and heated. Flow rates can be given up to 60L/min in adults with FiO2 varying from 21-100%. High-flow humidified oxygen should be considered when a patient is unable to maintain SaO2 ≥ 92% with standard oxygen delivery, despite conventional oxygen delivery at FiO2 > 6L/min or an FiO2 40%.,

Non-Invasive Ventilation

In patients with COVID-19 who are deteriorating, early endotracheal intubation and invasive mechanical ventilation should be considered. For those patients whom NIV is appropriate, for example, patients with concomitant COPD with type 2 respiratory failure, hypercapnoea and pulmonary edema, ensuring optimum airborne and infection control precautions is essential.

Prone positioning

For mechanically ventilated adults with COVID-19 and hypoxaemia despite optimum ventilation, prone positioning should be considered. There is evidence to suggest prone ventilation is effective in improving hypoxia. Suitable PPE for those delivering care to the patient should be ensured as well as efforts to minimise the risk of adverse events such as accidental extubation.[41]

Most COVID-19 patients who require mechanical ventilation have ARDS. Mechanical ventilation initiated with lower tidal volumes (4 to 6 ml/kg predicted body weight, PBW) and lower inspiratory pressures, reaching a plateau pressure (Pplat) < 28 to 30 cm H2O. PEEP must be as high as possible to maintain the driving pressure (Pplat-PEEP) as low as possible.

Extracorporeal membrane oxygenation (ECMO) for patients with refractory hypoxemia despite lung-protective ventilation should merit consideration

MODS in COVID-19 are multifactorial but include a hypercoagulable state with micro- and macro-circulatory thrombosis. Heparin may reduce thrombi in organ

microcirculation, most notably in the pulmonary vasculature. It has potential benefit over other anticoagulants due to its anticoagulant (decreased emboli in coronary, pulmonary vasculature and microvascular ischemia), anti-inflammatory (decreased lung inflammation and anti-viral properties. Heparin may possess anti-viral properties by acting on surface receptor binding proteins and inhibiting viral attachment.

As with all DIC cases, patients may progress to a hypocoagulable state when fibrinogen levels begin to decrease. At this point anticoagulation should be stopped.

- All COVID-19 Patients should be tested for coagulation studies at admission, in particular D-dimercoagulopathy later in their hospital course, routine serial measurements of coagulation studies
- All patients with COVID-19 should be placed on prophylactic doses of anticoagulation, preferably with LMWH, unless there is a contraindication, such as acute kidney injury (AKI), wherein
- Therapeutic anticoagulation should be given in high-risk for coagulopathy (including CRRT and ECMO), demonstrating signs of microthrombi-induced organ dysfunction, or with documented or strongly suspected macro-thromboembolism.

Preventative Measures for the General Public

Simple protective measures for the general public have been regularly advertised across media outlets throughout the COVID-19 pandemic. These have included measures such as social distancing (ensuring a minimum of one metre between yourself and another individual at all times), regular hand washing with soap and water (for a minimum of 20 seconds) and sanitising surfaces and objects that are regularly touched such as mobile phones, computer keyboards, house and car keys, etc.44 In addition to this, avoiding non-essential travel and human contact such as hugs and handshakes and staying home when exhibiting any cold and flu-like symptoms has been widely encouraged.

Preventative Measures in a Healthcare Setting

For those healthcare workers who are on the front line of the COVID-19 outbreak, there are specific measures that must be strictly adhered to in order to prevent infection transmission. Specific Personal Protective Equipment (PPE) that has been recommended by the World Health Organisation includes goggles (preferably with a good seal to the skin of the face), face shields, N95 or FFP2 respirator type masks, nitrile, powder-free gloves and disposable surgical gowns or aprons. It is important to note that surgical masks do not provide sufficient protection against COVID-19; their design is such that they offer protection to patients, however do not protect the wearer. Finally, it is important that adequate disinfection of patient surroundings, particularly following their discharge is strictly adhered to in order to prevent transmission via contaminated surfaces.[45]

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