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# Pathophysiology of SARS-CoV-2 (COVID 19) viral infection

Maanya Bhardwaj*

Jawaharlal Nehru Medical College, Datta Meghe Institute of Medical Science (Deemed to be University), Sawangi (Meghe), Wardha, Maharashtra 442004, India

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ABSTRACT

The city of Wuhan located in Hubei province of central China was burdened with a series of cases presenting with atypical acute respiratory infections in December 2019. Little did people know at that point in time, that a novel virus known as SARS-CoV-2 (COVID-19) or simply corona virus, was responsible for these peculiar presentations. COVID-19 had begun spreading at an alarming rate worldwide, eventually gaining official status as a global pandemic, as affirmed by the World Health Organisation (WHO) on 11 March 2020. By 6 July 2020, globally, there were 1.5 million cases and around 536 893 deaths. As the pandemic took its toll globally, scientists struggled to classify and specify the manifestations of the virus. Medical practitioners, microbiologists and scientists worldwide gradually joined forces to define COVID-19 as an infection characterised by an immense inflammatory reaction or cytokine storm which may cause acute respiratory distress syndrome (ARDS) and multi-organ dysfunction (MODS). During the latter half of 2020, multiple hospitals in India, France, America, Germany and Netherlands reported an increasing incidence of fatal invasive fungal infections in recovered SARS-CoV-2 patients. Increased severity of infections as well as mortality was observed in immunocompromised patients and those with co existing medical illnesses such as diabetes and hypertension. Furthermore, even though many patients recovered from SARS-CoV-2 infection, it was noted that their immunity post recovery was significantly diminished, and it was during this period they were more susceptible to fatal bacterial and fungal co-infections. This review article explores the pathophysiology of COVID 19 infection and difference in response to the infection in adult and paediatric populations.

*Corresponding Author

Name: Maanya Bhardwaj
Phone: 8551958894
Email: maanyab@gmail.com

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## INTRODUCTION

In December 2019, a novel virus wreaked havoc in the central Chinese province of Wuhan, ultimately leading to a global pandemic. The virus was identified as a novel corona virus known as severe acute respiratory distress syndrome corona virus 2 (SARS-CoV-2) owing to its genetic similarity to the SARS corona virus which led to an outbreak back in 2002 (World Health Organization, 2020). Generally, corona viruses which circulate between humans are benign, causing common cold related illnesses and flu. However, SARS-CoV-2 originated from bats (natural animal reservoir) and mutated to cause disease which had previously not been observed in

humans (Zhou *et al.*, 2020b). Transmission between individuals occurs primarily through direct contact and droplet spread, and this played a critical role in the rapid, global spread of the virus. Outbreak of the novel corona virus caused panic among populations and led to the development acute atypical respiratory disease. Consequently, several nations had to enforce strict lockdowns and social distancing measures to prevent further dissemination of the virus.

**General background**

SARS-CoV-2 predominantly involves the respiratory system (lower respiratory tract), although other systems may also be involved. Initial cases reported from Wuhan, revealed that patients complained of the following symptoms: fever, dry cough, dyspnea, loss of taste sensation, headache, fatigue, dizziness, vomiting and diarrhoea (Yuki *et al.*, 2020). A wide spectrum of respiratory manifestations of COVID-19 were reported, including minimal symptoms such as fatigue and severe hypoxia with acute respiratory distress syndrome. Epidemiological studies revealed increased mortality in the elderly population, immunocompromised patients, and patients with comorbidities such as diabetes and hypertension, whereas, incidence was much lower in younger age groups such as adolescents and young adults (Dhochak *et al.*, 2020). Currently, no specific treatment is available, and therapy is largely based on the management of symptoms. Scientists are also undertaking research to develop vaccines against SARS-CoV-2. To ensure safety, the vaccines are currently facing intense scrutiny from health organisations and are also being used for clinical trials before being made available to health workers and the general public.

**Epidemiology of covid-19**

Epidemiological data from studies in China illustrated that initially, COVID-19 cases were observed primarily in elderly populations (> 65 years of age) with no significant gender predilection and mean incubation period of 5.2 days (Yuki *et al.*, 2020). However, as the pandemic progressed throughout the world, in countries such as Italy, Spain, France, Germany and The United States of America, it became clear that there was a slight male predilection to COVID-19 (Wiersinga *et al.*, 2020). Male preponderance was attributed to a multitude of factors such as smoking and drinking alcohol which contribute to decreasing immunity. On the contrary, women are more likely to adopt protective behaviours such as frequent hand washing, correct use of masks, maintaining social distancing and avoiding crowded areas thus, adding to the slight male predilection (Wiersinga *et al.*, 2020). Furthermore, detrimental outcomes of COVID-19 were more common in patients with comorbidities including diabetes mellitus, high blood pressure and cardiovascular disease. These illnesses are prevalent in the male population as they commonly occur due to years of smoking and consumption of alcohol. As the disease progressed, it became clear that paediatric populations (< 18 years of age) were also affected but to a lesser extent (Dhochak *et al.*, 2020). Outcomes and prognoses were also much more favourable for paediatric patients as compared to elderly patients.

In mid 2020 scientists noticed the rising prevalence of fungal infection outbreaks observed in post covid recovered patients in health care facilities. The accelerated spread of fungal infections may have been precipitated by adoption of different infection control protocols in response to the SARS-CoV-2 pandemic such as modification of disinfection practises, scarce supply of personal protective equipment; gloves, masks, gowns and reuse of these items due to limited supply (White *et al.*, 2020).

A unique feature of COVID 19 infections is that lower proportions of affected patients were vulnerable to bacterial co-infections during the disease period as well as post recovery period in comparison to influenza pandemics in the past. Consequently, routine use of antibiotics is not indicated in COVID 19 patients.

**Mechanism of SARS-CoV-2 (COVID-19) invasion into host cells**

Corona viruses are single stranded enveloped RNA virus classified within Nidovirales order and are divided into four genera: alpha, beta, gamma and delta (Mason, 2020). Alpha and beta types are responsible for infecting mammals. The corona viruses responsible for croup and common cold belongs to alpha group, in contrast, corona virus responsible for SARS-CoV, Middle East respiratory syndrome corona virus (MERS-CoV) and SARS-CoV-2 belong to beta group (Zhou *et al.*, 2020a).

The virus enters the host cell via the 5 following mechanisms: attachment, penetration, biosynthesis, maturation and release (Wan *et al.*, 2020). During the initial stages, the virus binds to receptors on the surface of the host cell membrane (attachment), afterwards it undergoes endocytosis and enters the host cell (penetration). Viruses can also enter the host cell via membrane fusion. Viral contents enter inside the host cells and the viral RNA enters the nucleus of the host cell for the process of replication (Mason, 2020). Synthesis of viral proteins occurs from the viral mRNA which is present inside the host cell nucleus (biosynthesis), these viral pro-

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teins mature (maturation) and are released to infect other host cells (release). Corona viruses are composed of four structural proteins known as: spike (S), membrane (M), envelope (E) and nucleocapsid (N). The spike protein has two subunits. The S1 subunit binds to the host cell receptor and the S2 subunit plays a role in the fusion of membranes (Mason, 2020). Scientists later discovered that SARS-CoV-2 uses the Angiotensin converting enzyme 2 (ACE2) as its functional receptor (Bourgonje *et al.*, 2020). ACE2 receptors are expressed in high concentrations in the lungs, heart, kidney, bladder, and ileum. Thus, these organs are highly susceptible to infection by SARS-CoV-2.

**Host response to sars-cov-2 (covid-19)**

Manifestations of SARS-CoV-2 patients range from asymptomatic presentation to acute respiratory distress syndrome alongside multiple organ failure. ACE 2 receptors, the functional receptors for SARS-CoV-2 are highly concentrated on the apical side of type 1 pneumocytes within the alveolar space. Consequently, SARS-CoV-2 is likely to invade and destroy these cells (Parasher, 2020). This correlates with findings that early lung injury in COVID-19 is most likely to involve the distal airways. Epithelial cells, dendritic cells (DCs) and alveolar macrophages are the three predominant cell types which are integral in maintaining the innate immunity of the airways (Yuki *et al.*, 2020). However, dendritic cells and alveolar macrophages are located near the lung epithelial cells, therefore, serving the primary purpose of defence against SARS-CoV-2 until adaptive immunity intervenes.

Proposed mechanisms of immunity against COVID-19 include phagocytosis of infected alveolar cells in the lung epithelium via dendritic cells and alveolar macrophages. The apoptotic virus laden epithelial cells are phagocytosed by dendritic cells and alveolar macrophages with antigen presentation occurring to T cells (Kordzadeh-Kermani *et al.*, 2020). After phagocytosis of the virus, dendritic cells and alveolar macrophages express viral antigens on their surfaces and travel to the nearest draining lymph node for presentation to T cells. Both CD 8 and CD 4 cells play an important role in immunity. CD 4 cells are responsible for stimulation of B cells for production of virus specific antibodies, whereas CD 8 cells act by killing the virus-infected cells. Further research needs to be undertaken as it is unclear whether dendritic cells and macrophages are primarily infected by the virus. Pro-inflammatory cytokines, including interleukin six (IL-6), interleukin ten (IL-10), granulocyte-colony stimulating factor (G-CSF), monocyte chemoattractant protein 1 (MCP1), macrophage inflammatory protein (MIP)1$\alpha$ and tumour necrosis factor (TNF)-$\alpha$ were noted to be increased in the plasma of patients suffering with severe disease (Yuki *et al.*, 2020). Increases in IL-6 levels directly correlated with the severity of disease. CD4and CD8 T cells were activated in these patients, which was evidenced by raised levels of CD 69, CD 38 and CD 44 markers (Hoffmann *et al.*, 2020).

Studies of patients with SARS-CoV-2 demonstrated epithelial cells which are viral hosts produced both IL 8 and IL 6. Interleukin 8 functions by attracting neutrophils and T cells to the site of infection in addition to stimulating angiogenesis. A large amount of inflammatory cell infiltrate was seen in the lungs of patients suffering from severe disease with the cells predominantly consisting of a mosaic of innate and adaptive immune cells (Mason, 2020). A significant amount of the innate immune cells were found to be neutrophils.

Neutrophils are simultaneously the first line of defence against a pathogen and inducers of lung injury due to toxic free radicals produced during destruction of pathogens. Most of the infiltrating adaptive immune cells were found to be T cells which correlated with the fact that there was a significant decrease in circulating T cells suggesting lymphopenia. Similarly to neutrophils, cytotoxic T cells are able to kill viruses but are also involved in producing lung injury in the process of killing.

It was interesting to note that CD 14and CD 16 cells, which are rarely found in healthy individuals were also significantly raised in infected patients (Yuki *et al.*, 2020). These inflammatory CD 14 and CD 16 monocytes expressed IL-6 at a higher level, resulting in an increased rate of progression of a systemic inflammatory response which most likely accelerated the progression of systemic inflammatory response.In some cases, severe COVID-19 infections have manifested with thrombosis and pulmonary embolism in addition to respiratory symptoms. Positive D dimer and fibrinogen tests in patients with severe disease demonstrate that there are thromboses present in the body, which correlates with the findings (Kordzadeh-Kermani *et al.*, 2020).

Thrombotic regulation by the endothelium is disturbed in severe disease, leading to a hypercoagulable state seen which demonstrates significant endothelial injury. One third of lung cells are compromised by endothelial cells with these endothelial cells expressing ACE 2 receptors (Kumar and Khodor, 2020). Damage to the endothelial cells can make the cells more susceptible and vulnerable to invasion by the virus.

**Impact of cytokine storm in covid 19 patients**

Cytokines are small protein molecules which are soluble and act as messenger for immune cells present in our body. The production of cytokines takes place in various immune cells of the body such as eosinophils, neutrophils, basophils, mast cells, dendrites, monocytes macrophages, B cells and T cells. Cytokines have the ability to influence activities of the cell such as maturation, activation of immune cells, changing expression of genes, growth and development. COVID 19 patients experiencing a mild form of the illness may spontaneously become severely ill due to the development of a "cytokines storm". Cytokines play a protective role in the body's immune response against infections and are crucial for viral clearance, however, studies conducted on COVID 19 patients admitted in the intensive care unit illustrate excessively high concentrations of pro inflammatory cytokines, specifically, interleukin 6 (IL 6) in comparison to patients experiencing a mild form of the illness. COVID 19 infection specifically induces macrophages to produce interleukin 6 which accelerates lymphocyte necrosis and chemotaxis of neutrophils to the site of inflammation (Tang *et al.*, 2020). Laboratory studies of SARS-CoV-2 infected patients showed that peripheral blood mononuclear cells indicated non structural protein 9 (nsp 9) and non-structural protein 10 (nsp 10) of corona virus target NKRF (NF-$\kappa$B repressor) to promote interleukin 6 (IL-6) and interleukin 8 (IL-8) production which leads to recruitment of neutrophils and exacerbates uncontrollable host inflammatory response (Tang *et al.*, 2020). The hyperactive host immune response towards virus antigens leads to excessively high levels of cytokines which in turn are responsible for the apoptosis of endothelial and epithelial cells. Subsequently, there is loss of integrity of vessels causing vascular leakage ultimately leading to acute respiratory distress syndrome, shock, multi system failure and death. Increased levels of cytokines are suggestive of a poor prognosis in SARS-CoV-2 infection.

Furthermore, SARS-CoV-2 promotes infection of $CD169^{+}$ macrophages situated in lymphoid tissues such as spleen and lymph nodes eventually causing destruction as evidenced by atrophy of splenic nodule and depletion of lymph follicles. $CD169^{+}$ macrophages lead to activation-induced cell death (AICD) via interactions of Fas with Fas L (Tang *et al.*, 2020). In addition, post-mortem evaluation of lung tissues of COVID 19 infected patients has shown infiltration of pro inflammatory cells such as T helper 17 cells and macrophages. Tocilizumab (TCZ) is an IL-6 receptor monoclonal antibody, antagonising the binding of IL-6 to its receptor, consequently averting the immunosuppression caused by IL-6 and thus, potentially leading to clinical recovery (Tang *et al.*, 2020). TCZ has been proven to be a safe drug and may even be utilised in patients with other comorbidities such as sickle cell disease, multiple myeloma, end stage renal disease and many more. In addition, TCZ was found to significantly decrease levels of inflammatory markers such as C-reactive protein (Tang *et al.*, 2020). Administration of TCZ in patients of SARS-CoV-2 infection revealed betterment of symptoms such as respiratory function and fever within a short period of time. Intravenous immunoglobulins (IVIG) provoke the development of passive immunity and anti-inflammatory effects by neutralising antibodies, this is crucial in promoting survival in severe infection and acts as an adjuvant to routine treatment.

**Fungal infections in covid 19 patients**

Recently, new evidence has come to light that fungal infections may be linked with COVID-19. Fungal infections, also known as mycoses, are contracted via inhalation of fungal spores or local colonization of the skin. For this reason, fungal infections present with respiratory or integumentary symptoms. Therefore, fungal infections symptoms can often mimic COVID-19 symptoms, which include pyrexia, persistent cough and dyspnoea. Perhaps more importantly, some patients who are severely ill with COVID 19 can simultaneously have fungal co-infections (Kuehn, 2020). Patients who are admitted to ICU are at a significantly increased risk of contracting a fungal infection from organisms including aspergillus or candida (Talento and Hoenigl, 2020). Aspergillus in particular is known for causing respiratory infections, otherwise known as pulmonary aspergillosis, whereas candida most commonly causes vaginal yeast infections, skin infections and oral thrush. Co-infection of these organisms with SARS-COV-2 leads to increased severity of the illness and increased mortality.

Historically, Aspergillosis almost only occurred in immunocompromised individuals, however, new observations have shown that patients with severe COVID-19 infections who were otherwise immunocompetent have also contracted aspergillosis. This is known as COVID-19 associated pulmonary aspergillosis (CAPA). CAPA is more frequently reported in patients who are on ventilators due to a severe covid-19 infection. This is a very dangerous complication as it can rapidly cause deterioration of the patient as seen through the development of sepsis and declining pulmonary function. The proposed pathogenesis of CAPA theorizes that an exacerbated immunological response, triggered

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by the release of danger associated molecular patterns (DAMPs) as a result of Aspergillus induced inflammation leads to lung damage, consequently causing acute respiratory distress syndrome (Lansbury *et al.*, 2020). Risk factors for development of CAPA include broad-spectrum antibiotic use, which allows for opportunistic growth of aspergilla, use of corticosteroids in patients with acute respiratory distress syndrome, which causes immunosuppression and patients who are suffering from other comorbidities.

Candidiasis is a yeast infection which commonly occurs in the mouth (oral thrush) and in the vagina (vaginal thrush). This is different to invasive candidiasis, which is significantly more severe and potentially life-threatening. This is because it involves the heart, brain, eyes, bone, with dangerous manifestations such as endocarditis, osteomyelitis and meningitis. It has been observed that candida infections tend to be nosocomial in the context of COVID 19 patients, occurring due to the use of broad-spectrum antibiotics, which allows opportunistic growth of the fungi, or in cases where a central venous catheter was used (Nestler *et al.*, 2020). Patients in intensive care unit are already unwell, however they are also subject to invasive procedures such as catheterization, which provides a route of entry for candida.

### Difference in response to covid-19 in adult and paediatric populations

Generally, infants and young children are susceptible to respiratory infections with pathogenic agents including the influenza virus and the respiratory syncytial virus, consequently requiring hospital admission (Dhochak *et al.*, 2020). On the contrary, paediatric COVID-19 patients have relatively milder symptoms and most of the times do not require hospitalisation. It is unclear as to what exactly leads to the difference in response to the virus in the adult and paediatric populations, however, reports suggest that the disease severity and viral load (duration of virus shedding period) are linked. Children possibly have decreased viral loads despite being COVID-19 positive in comparison to adults (Dhochak *et al.*, 2020).

Another possible explanation to the difference in response to viral infection between adult and paediatric populations could be due to varying levels of expression of ACE 2 receptors in lung epithelial cells. ACE2 receptors have an increased expression in pseudostratified, ciliated columnar pulmonary epithelial cells which are highly differentiated (Parasher, 2020). The human lung epithelial cells undergo continuous development following birth; therefore, ACE 2 receptor expression is likely to be lesser in paediatric populations compared to adult populations. In addition, gender also affects levels of ACE 2 receptor expression, resulting in men having a higher severity and mortality. This is because the ACE 2 receptor gene locus is within the X-chromosome (Leap *et al.*, 2020). Furthermore, men have a higher level of circulating ACE2 receptors compared to women. This is theorized to be the reason for the variation in severity and mortality between males and females in both adult and paediatric populations. Another theory which has been suggested is the concurrent presence of additional viruses in airway and lung mucosa of children which can compete with SARS-CoV-2 virus and prevent its dissemination.

## CONCLUSION

A multitude of factors and combination of the above possibilities may result in an improved insight into the different presentation of SARS-CoV-2 infection in paediatric and adult populations. This understanding and awareness may help guide scientists in developing appropriate vaccines and immunotherapy in order to halt the progression of this pandemic and eradicate the virus.

### Conflict of Interest

The authors declare that there is no conflict of interest.

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