The Immune System's Battle Against SARS-CoV-2

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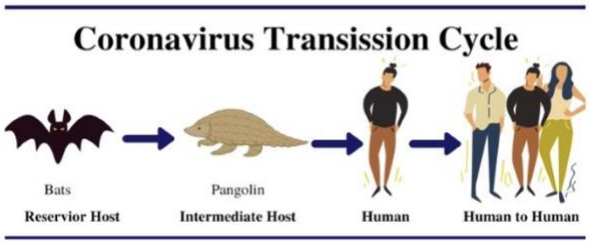
I. ABSTRACT

The widespread public health and safety implications of the spread of SARS-CoV-2, a viral respiratory disease, have been witnessed worldwide. The immune system is an integral component in both the recovery progression and the severity of illness in individuals who contract coronavirus. Complications in the immune system due to SARS-CoV-2 have led to the development of Multisystem Inflammatory Syndrome in Children (MIS-C), which has shown to be a rare, but serious disease. MIS-C is a condition causing severe inflammation in children after exposure to COVID-19, with symptoms including vomiting, skin rash, and redness. In this paper, we consider the components of the coronavirus immune response on the progression of illness severity and the development of MIS-C.

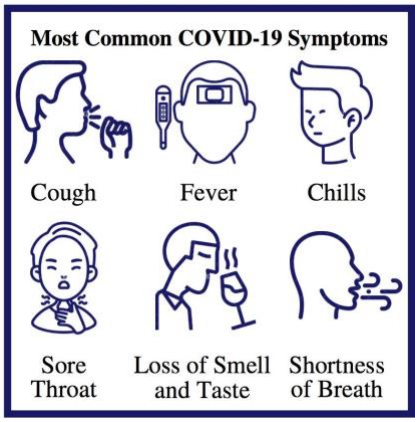
II. INTRODUCTION

The novel coronavirus 2019 (COVID 19) outbreak initially began in Wuhan, China in December of 2019. Due to phylogenetic similarities to severe acute respiratory bat viruses, bats have been connected to SARS-CoV-2 (COVID-19) as the primary reservoir host. Further investigations using molecular and phylogenetic analyses have determined a correlation between pangolin-CoV-2020 and SARS-CoV- 2. Although SARS-CoV-2 did not directly emerge from pangolin-CoV-2020, a genetic relationship has been linked between the pangolin virus and the coronavirus impacting the human population[1]. Through this conclusion and the indication of bats as the reservoir host which are similarly linked to pangolins, the intermediate host of SARS-CoV-2 has been hypothesized as the pangolin from which humans contracted the virus (Figure 1).



Based upon the phylogenetic correlations found between SARS-CoV-2, pangolin-CoV-2020, and similar SARS bat viruses, the hypothesized Coronavirus Transmission Cycle is pictured above.

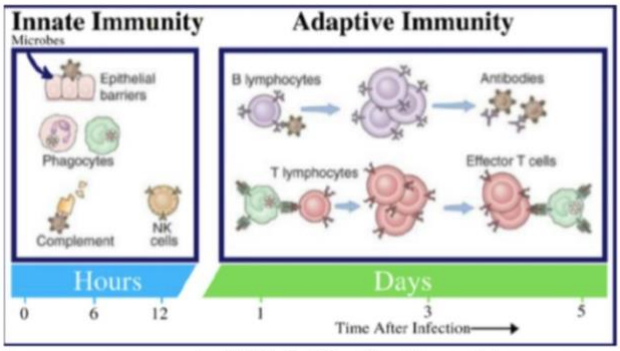
Those infected with COVID-19 have presented a wide range in severity and associated symptoms, beginning two to fourteen days after initial viral exposure. Symptoms of lesser severity include: fever or chills, cough, shortness of breath or difficulty breathing, fatigue,
muscle or body aches, headache, new loss of taste or smell, sore throat, congestion or runny nose, nausea or vomiting, or diarrhea. Symptoms warranting immediate medical attention include: trouble breathing, persistent pain or pressure in the chest, new confusion, inability to wake or stay awake, or blue-tinted lips or face.[2] These symptoms vary among patients in regards to the effectiveness of their holistic immune response.



Even with emergency containment efforts after initial reports of human cases, the virus spread throughout

metropolitan areas of China and eventually cases emerged across the globe. The current rate of infection has continued to drastically increase in the United States, while substantially lessening in other countries such as New Zealand. As of November 21, 2020, the total number of US cases has surpassed 11.8 million and the cumulative number of deaths has risen to 253,600[3]. The positive rate of daily increase in cases indicates that the public health threat posed by COVID-19 continues to persist and will likely remain in the near future.

III. INNATE VS ADAPTIVE IMMUNE SYSTEM



Immune responses to SARS-CoV-2 utilize the rapid response provided by innate immunity. The differences between the innate and adaptive immune responses are vastly evident as adaptive immunity mainly enables protection against antigens with B cells and T cells (both white blood cells). Whereas, the innate response is mainly for the incoming pathogen that appears on the surface of the skin or travels in depth into the airways. In those cases, phagocytes like monocytes, macrophages, neutrophils, and mast cells depicted above attack SARS-CoV-2 as "special" white blood cells. The similarity between these two responses lies with the natural killer cell which helps fight off the virus within the first few hours.

Individuals infected with SARS-CoV-2 have two types of immune systems to combat the disease and make up a possible recovery: the innate and adaptive immune response. The immune system's main role is to prevent or limit the spread of any sort of pathogenic germs or infectious substances detected on the skin, in the tissues of the body, or in bodily fluids.

The innate (general) immune system focuses directly on germs entering the body and is responsible for their elimination within 0-96 hours upon first contact. It is activated by the chemical properties of foreign antigens and includes cellular responses from macrophages, neutrophils, eosinophils, basophils, dendritic cells, and mast cells. It mainly offers protection through skin and mucous membranes as it provides a shield against antigens along with certain enzymes, defense cells, and killer white blood

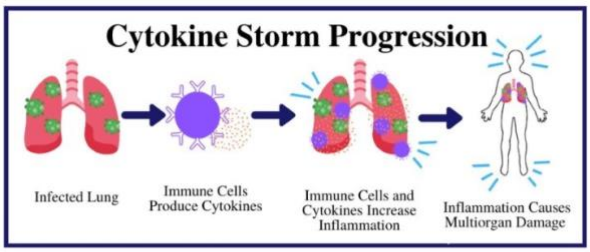
attributed to T helper cells that "memorize" pathogenic antigens from previous infections. The T white blood cells activate the B lymphocytes, which produce abundant amounts of necessary antibodies that neutralize bacteria and viruses through the activation of certain enzymes[4].

The localization of both components of the immune system are vital as each location serves a purpose in initiating the immune system; protection is spread across the skin which is placed as the first line of defense against foreign substances or germs. Bone marrow contains stem cells, which develop into immune cells for the immune system to begin fighting the pathogens. The blood stream circulates these produced immune cells waiting for them to be recruited by the cytokines to attack the pathogens. The thymus is where T lymphocytes mature before fighting viruses. The lymphatic system and spleen acts as a communication hub between bloodstream and tissues, and immune cells activate and respond when pathogens are recognized[4]. The mucosal tissue is the main entry point for pathogens with immune hubs storing white blood cells. All these areas in which the immune system's components rest strengthens the effectiveness of the immune system response as different parts of the response come into action depending on where the foreign pathogens reach.

SARS-CoV-2 imposes a dysregulated immune response known as cytokine storm or cytokine-release syndrome in patients infected with SARS-CoV-2. The cytokine-release syndrome develops into severe acute respiratory

Cytokines	Role	Symptoms
IL-1	Regulates immune and inflammatory responses to infections	Inflammation, respiratory failure
IL-6	Produced in response to tissue damage and infections	Inflammatory response, respiratory failure
IL-12	Downregulates allergic inflammation when released	Generates specific cytotoxic CD8+ T cells
IFN-γ	Stimulates natural killer cells and neutrophils, activates macrophages, mediates antiviral and antibacterial immunity, enhances antigens	Risk factor for lung fibrosis
TNF-α	Produced by macrophages during acute inflammation and is responsible for a range of signaling events within cells during an infection	Potential factor of toxic epidermal necrolysis

distress syndrome that pro-inflammatory cytokines, including IL-1α, IL-1β, IFN-α, IL-17A and IL-12 p70, inflict on the airway tract[5]. The presence of these cytokines has been reported in all patients infected with COVID-19. Furthermore, other cytokines including IFN-λ, thrombopoietin, IL-21, IL-23 and IL-33, were up-regulated in patients with severe symptoms of COVID-19. Moreover, these severe cases also reported molecules associated with defense response to viral infection released



Caption: After SARS-CoV-2 infects the lungs, immune cells produce cytokines to try and restore homeostasis in the body. When the immune system doesn't respond properly, an accumulation of immune cells and cytokines results in the infection site. As these immune cells and cytokines continue to be produced, they become widespread throughout the body, causing inflammation and lung injury, eventually leading to multi-organ failure.

by a type of activated CD4 T-cell called a TH1 cell. Patients with severe disease from SARS-CoV-2 were associated with the activation of a protein complex called the inflammasome which results in an immune response that causes inflammation. IL-1Ra, a protein that normally inhibits excessive inflammasome function, was seen in these patients and this up-regulated molecule dampens the immune response making SARS-CoV-2 stronger than the immune system[5].

IV. Healthy Versus Dysfunctional Immune Response

A healthy adaptive immune response to SARS-CoV-2 would typically help decrease the viral load and cause minimal damage that eventually leads to recovery. Part of this process involves the production of pro-inflammatory cytokines by several immune cells including innate macrophages, dendritic cells, natural killer cells, and T and B lymphocytes that then recruits monocytes, macrophages, and T cells from the surrounding blood to the site of infection.[6] Typically, the infected cells are cleared before the virus spreads and circulating antibodies neutralize the virus. The neutralized viruses are then recognized by alveolar macrophages and engulfed by apoptotic cells.

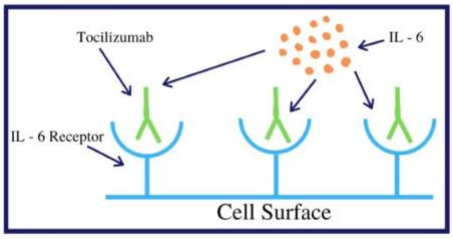
On the other hand, if an immune response to SARS-CoV-2 is dysfunctional, there are too many pro-inflammatory cytokines produced. This in turn causes an excessive accumulation of monocytes, macrophages, and T cells, in addition to the pro-inflammatory cytokines.[6] This exaggerated immune response is known as the cytokine storm where large amounts of inflammation lead to multi-organ damage and other complications that could result in death. The understanding of specific pro- inflammatory cytokines involved in the cytokine storm aids in finding strategies that will increase the survival rates of patients with SARS-CoV-2.

V. Types of Proinflammatory Cytokines

Interleukin-6 (IL-6) is a type of cytokine that plays a prominent role in the cytokine storm associated with SARS-CoV-2.[7] More specifically, IL-6 regulates the acute phase response in which the body increases inflammation in order to restore homeostasis after the entry of the SARS-CoV-2 pathogen that binds to the ACE-2 receptor. IL-6 also may be responsible for activating CD4+ T cells, or Helper T cells. While these cells help activate B cells and CD8+ T cells that help to directly kill infected cells, they also cause more pro-inflammatory cytokines to be produced, which continues to exacerbate the cytokine storm that becomes widespread in the body.

Interleukin-6 (IL-6)	Neuropathic Pain, Tactile Aldonyia
Tumor Necrosis Factor-Alpha	Hyperalgesia & Increased Pain Sensitivity
Chemokines	Neuropathic Pain, Neuroinflammation

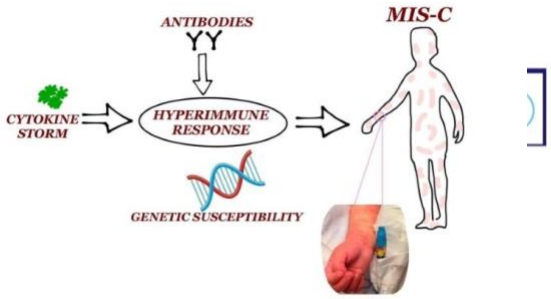
Elevated levels of IL-6 are associated with a higher rate of mortality and is the most commonly reported elevated level of cytokine in patients with SARS-CoV-2. Tumor Necrosis Factors are another type of cytokine that causes an inflammatory immune response and is responsible for producing Interleukins which have been identified as major pro-inflammatory cytokines. Other subgroups of cytokines that induce inflammation include chemokines which are unique due to how selective they are when recruiting immune cells to the site of infection.[7] Increased levels of any of these cytokines could be indicative of severe disease being present in the patient that needs to be treated immediately. The figure above highlights the associated symptoms that accompany increased levels of the aforementioned cytokines that are present both during initial infection and even have been identified after the patient no longer is infected.[14] In order to target these pro-inflammatory cytokines, strategies are being implemented in order to inhibit cytokines from attaching onto cytokine receptors on the surfaces of cells. The immunosuppressive drug Tocilizumab shown in the figure below targets Interleukin-6 to reverse the harmful effects of the cytokine storm.



Caption: Tocilizumab, an immunosuppressive drug that has been approved by the FDA for use in severe COVID-19 pneumonia works by targeting Interleukin-6 (IL-6), a proinflammatory cytokine. Tocilizumab attaches to the IL-6 cytokine receptors on the surfaces of cells to stop the transduction pathway, preventing many of the harmful effects of the cytokine storm.

VI. Multisystem Inflammatory Syndrome in Children

Multisystem Inflammatory Syndrome in children (MIS-C) is a condition in which causes severe inflammation on bodily parts including the heart, kidneys, digestive system,



MIS-C occurs when there is a hyperimmune response, a high concentration of antibodies that are produced due to the presence of an antigen, in the body. As a result, in addition to the cytokine storm and the build-up of antibodies, it results in an inflammatory response that prompts severe reactions to the body. Inflammation of organs as well as failure of them acn result. Research is still being conducted in order to understand more about genetic susceptibility and how this correlates with the severity of MIS-C, as certain genetic factors may make individuals predisposed to this condition. ***Inspired by a graphic by the MDPI and patient photo from the American Academy of Pediatrics

brain, and other organs. It can target children who are two to fifteen years of age, and this syndrome has not been reported to affect babies. Symptoms of inflammation on such body parts include redness, swelling, heat, and pain. Children who undergo this rare condition have been exposed to COVID-19, as shown by antibody tests with positive results. These positive results demonstrate that the child's immune system[8] developed antibodies, blood proteins that counteract antigens, which were created in response to the COVID-19 virus. However, a child diagnosed with MIS-C does not always develop the symptoms of COVID-19; the exposure of the COVID-19 virus can result in patients being asymptomatic, in which they never develop symptoms at all. On the other hand, there have been cases in which children developed the symptoms for the COVID-19 virus[9] and have developed MIS-C.

VII. Signs and Symptoms

The signs and symptoms of MIS-C include vomiting, skin rash, red eyes, redness or swelling in the hands or feet, fever, difficulty breathing, and severe stomach pain. After a child is exposed to COVID-19, the syndrome can develop within four weeks. If a child developed symptoms such as these, it is imperative to take immediate action and seek treatment.[10]

MIS-C has similar symptoms to Kawasaki Disease (KD), a disease in which it involves the inflammation of blood

vessels that causes artery aneurysms. KD specifically affects children who are younger than five years old, and the exact cause of it has not been determined yet. It may be linked to certain environmental exposure and genes, but scientists are continuing research on this syndrome. It is still unknown whether MIS-C and Kawasaki Disease are linked in any way, but further research is allowing scientists to develop new treatments for MIS-C due to the similar symptoms.[11]

VIII. Treatment and Prevention

The treatment of MIS-C includes going to a pediatric hospital in which health professionals check for areas of inflammation in bodily organs by doing tests of the chest, heart, and abdomen. Anti- inflammatory drugs are used in order to help mitigate internal inflammation in vital organs and to reduce multi-organ failure. Although MIS-C is not contagious, children infected with COVID-19 may still transmit[12] SARS-CoV-2 to other susceptible individuals which could potentially lead to the development of MIS-C. As a result, it is important to enact proper guidelines to prevent the spread of COVID-19 so less cases of MIS-C may arise.

Certain prevention measures for MIS-C that have been outlined goes in tandem with COVID-19 prevention measures. Washing hands frequently, practicing social distancing, wearing masks, and avoiding people who are sick allows for the spread to slow down and for the disease to not infect as many individuals. Since COVID-19 and MIS-C are still new topics of discussion for researchers, there are many intricacies that are still unknown. However, by taking precautionary measures in order to avoid any harm, it creates foreseeable benefits.

IX. Conclusion

In efforts to overcome this immensely riddling virus that overtakes the immune system, researchers and scientists have been working on developing any form of treatment or vaccine that they can. When such a virus is equipped with capabilities to mutate and can destroy existing antibodies or leading to Acute Respiratory Distress Syndrome (ARDS) in patients and MIS-C in young children, a vaccine is in dire need. Research and development is currently in progress in order to help with the treatment of COVID-19. Recently, a new drug by the name of Remdesivir has entered the market with a high price for hospitals. This drug, however, appears to work efficiently against SARS-CoV-2 by blocking the coronavirus's RNA polymerase using a nucleoside analogue of adenosine which is one of the main enzymes that SARS-CoV-2 needs to replicate its genetic material[13]. Dexamethasone which is a common corticosteroid medication that has been used for many years to treat various health conditions including autoimmune conditions. Hydroxychloroquine and chloroquine are two drugs that usually treat malaria, rheumatoid arthritis, and lupus, and Azithromycin which is an antibiotic commonly used to treat bacterial infections such as bronchitis and pneumonia and has been shown to have some in vitro activity against influenza A and Zika, but not Middle East Respiratory Syndrome, also known as MERS (another coronavirus). More treatments are in the works with immunology, with possibilities to use stem cell derived heart cells to treat the infection of heart cells, to support the immune system's battle against SARS-CoV-2

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