COVID-19 : A RETROSPECTIVE MINI REVIEW ON THE PANDEMIC VIRUS, IMMUNOLOGICAL ASPECTS AND BACTERIAL CO-INFECTIONS

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Abstract:

In 2019 the Corona pandemic spread in Wuhan City, Hubei, China. It is a disease officially known as "coronavirus disease 2019; COVID-19", which is the pathogen of respiratory tract infection and its genome sequence have been fully identified. The genetic sequence of COVID-19 showed a similar but distinct genome content for both SARS-CoV and MERS-CoV.

Clinical evidence and genetics point to the course of this pandemic. Open access data and genomic sequencing combined with the development of a specialized vaccine against infection with this virus, it will give us additional information about what this virus is, the nature of the immune response generated against it and plan for the herd immunity by vaccination. In current study, we review the role of innate and acquired immunity against COVID-19 and how it works in the host's body. Then, talk about herd immunity and how can reach it to protect the population from this virus. Also, focused in this review on associated bacterial infections with viral respiratory infections.

Key words: COVID-19 Pandemic, Immune Response, Herd Immunity, Co-Bacterial İnfections.

http://dx.doi.org/10.47832/MinarCongress6-41

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Introduction:

Because the infection with COVID-19 is a battle of the virus against the immune system of the infected individuals, therefore we must take a long look at this battle. The infection with coronavirus disease 2019 was discovered and disease broke out in December 2019 , Wuhan city, China. The virus spread through Chinese cities quickly and moved from them and became a global epidemic. As a viral infection of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that infected 3.6 million people in May 7, 2020, corona virus caused 254,045 deaths globally, and almost 200 countries where the pandemic has spread (Prompetchara *et al.*, 2020). What is remarkable of COVID-19 is the rapid spread of the disease in less than 3 months and has become a pandemic, and keep searching to find out how strong and how long this protection remain, while most people with COVID-19 develop an immune response within the first few weeks after infection. The World Health Organization, (2021) also, research focused on the idea that the length and strength of the immune response, does it vary according to the nature of the infection? whether it was strong, moderate, mild or completely asymptomatic (Prompetchara *et al.*, 2020).

When a population was immunized through previous infection or immunity progress through vaccination, this indirect protection from infectious disease known as population immunity or Herd immunity. The World Health Organization, (2021) encourages obtaining herd immunity by taking the vaccine, and does not support the idea of obtaining it through exposure to a disease or pathogen and does not allow the disease to spread among any segment of society, resulting in unnecessary infections and possibly deaths (Harrison *et al.,* 2020). In order to protect individuals infected with COVID-19, and to achieved herd immunity should be adopted the vaccination, this is a typical way for protection, not by direct exposure to pathogen and causes disease. Vaccines enhances the immune system to create specific immunoglobulins against the virus, exactly as happened when exposure to real pathogen, vaccines working without causing diseases (Liu *et al.*, 2020 ; Gebrecherkos *et al.*, 2022).

Host-pathogen interaction

The transmission mode of COVID-19 occur through close contact of people or from person to person by respiratory droplets (Letko *et al.*, 2020 ; Varghese *et al.*, 2020). Clinical signs of infection were unclear or non-specific and slowly appeared (Bao *et al* ., 2020). One of the important observations accompanying infection with this virus that most of the infected people did not exposed to markets or been in close contact with patients have respiratory symptoms. The highly contagious nature of

COVID-19 is due to its transmission through asymptomatic infected persons (Chan *et al.*, 2020 ; WHO, 2020).

COVID-19 Immunopathology

Although, the initial site of COVID-19 infection is still under investigation, but because it is a respiratory viral agent for most patients, it colonize only the lungs. After transmission of virus through direct contact with infected persons via sneezing or coughing, there is a 14 days of asymptomatic incubation period, during which the virus can be transmitted to another individuals (WHO, 2020). The multi-organ failure that increased in elderly and people have chronic diseases like diabetes, hypertension, cardiovascular disease raising death rates worldwide (WHO, 2020). COVID-19 made contacts and binding interface with specific receptor ACE2 (angiotensin converting enzyme 2) and have affinity for interaction with the host cells (Shang *et al.*, 2020). Spikes present on the surface of the virus it can enter the host's cells by binding to the ACE2 receptor (Walls *et al* ., 2020). Then replication cycle was started, with limited innate immune response from the patient. As the virus continues to multiply and colonize the respiratory system, where it experience a stronger innate immune response. Clinically, disease signs appears at this stage, about 80% of the infected patients have mild disease symptoms, mostly restricted to the upper respiratory pathways (Wu *et al.*, 2020). With appropriate symptomatic treatment, patients can be monitored at home. Some of patients may developed pulmonary infiltrates, others can complicated very severe diseases. Age is an important and influencing factor for patients with severe cases, elderly patients in the severe group have chronic diseases such as coronary heart disease, hypertension, chronic pulmonary disease, malignant tumor, and chronic kidney disease were more frequent than in the mild group, so patients over 60 years old age having comorbidities, like hypertension were at the risk of severe infection with the virus, as well as death (Wang *et al.*, 2020).

Innate immune responses to COVID-19

Cellular immune response represented by T- lymphocytes play a role inside the infected cells, through clearance viral-infected cells by cytotoxic T- cells (Lu *et al.*, 2020).

In Wuhan, through a study that investigated more than 90 case, observed an increase in neutrophils (38%), reduced in lymphocytes (35%), an increase in serum IL-6 (52%) and in c-reactive protein (84%). Increased neutrophils (Lee *et al.*, 2004),

decreased lymphocytes and higher plasma levels of many innate cytokines, all the previous findings may lead to elevated rate of disease and death (Zhou *et al.*, 2020). According to comparison between pro-inflammatory cytokines of mild and severe cases under monitoring, it noticed that IL-1 have an important role in increasing pathogenicity (Blanco-Melo *et al.*, 2020). In mild infections of COVID- 19 pro-inflammatory cytokines were not elevated, that proved a high level of pro-inflammatory response was a clinical finding of severe infection (Blanco-Melo *et al.*, 2020).

The influx of neutrophils and monocytes / macrophages results in hyper-production of pro-inflammatory cytokines (Magro *et al.*, 2020). The immunopathology of lungs may be the result of the "cytokine storms". Specific Th1 / Th17 may be activated and contributed to exacerbate inflammatory responses. B cells / plasma cells produce COVID-19 specific antibodies that may help neutralize viruses (Shokri *et al.*, 2019).

Adaptive immune response against COVID-19

Immune system cannot react properly when the body first encountered germs or viruses and the body get sick, the same thing were happened when first infected with COVID-19 (Kumar *et al.*, 2020). After infection with virus, immune system response mediated by antibodies production, by assistance of T- cells, B- cells were differentiate into plasma cells, which in return produce antibodies specific to a viral antigen. The neutralization process achieved by the antibodies were effective in preventing the virus from invading other host cells (Chen *et al.*, 2022), then restrict the infection. In later stages of infection, antibodies play an protective role, it may provide protection against recurrence of the infection in the future, adaptive immune response which play essential role in clearance of COVID-19 by:

a. cytotoxic T-cells activation that destroy infected cells with virus.
b. B-cells that produce neutralizing antibodies against virus-specific antigens.

One of the distinguishing characteristics of COVID-19 infection is blood lymphopaenia, with decrease in production levels of B-cells, CD4+ T-cells, and CD8+ T-cells (Boix and Merino, 2022). An abnormal innate immune response occurs in blood lymphopenia, characterized by decreased IFN-I production, which play a role in antigen presentation through assembly of viral material, that lead to enhancement of adaptive immunity (Liu *et al.*, 2017). Other mechanisms also present like, infection of T-cells by COVID-19 directly, MAS-related haemophagocytosis, cytokine induced apoptosis and pyroptosis of lymphocytes, lymphocyte sequestration in the lungs or other organs, reduced bone marrow hematopoiesis, and virus induced tissue damage

of lymphatic organs. All previous symptoms associated with COVID-19 lymphopaenia (Kaneko *et al.*, 2020 ; Zhang *et al.*, 2020).

A high percentage of COVID-19 patients, whose infections ranged from mild to moderate, showed potent adaptive immune response consisting of neutralizing antibodies and T-cells that lasts for months after first infection (Bradley *et al.*, 2020 ; Liu *et al.*, 2020). COVID-19 antigens are processed by antigen-presenting cells (APCs), that migrate to the lymphoid system and enhances immune response, leading to antigen recognizing then, proliferation and differentiation of T-lymphocytes leading to produce CD4+ and CD8+ (Tillett *et al.*, 2021).

T-lymphocytes also responsible for infected cells clearance (CD8+ cytotoxic T-lymphocytes), cytokine production, and activation of naïve B-lymphocytes (Wajnberg *et al.*, 2020). Humoral immunity represented by B-lymphocytes that subsequently generate large numbers of neutralizing immunoglobulins. On the other side, induction of cytokines occur in huge numbers, leading to hyper inflammation, as constituents of the 'cytokine storm' in severe disease (Soares-Schanoski *et al.*, 2022). Cytokines that contributed in cytokines storm e.g. IL-6, TNF-α, IL-1β, IP- 10, MCP-1, CSFs, and IL-17A. While those e.g. IL-15, IFN-α, IL-12, IL-21, and IFN-γ are essential in viral clearance in mild to moderate cases (Zuo *et al.*, 2020).

In severe cases of COVID-19, immune cells were distinguished by dysfunction, high levels of neutrophils and monocytes production with decreased levels of effector T-lymphocytes (Rydyznski *et al.,* 2020 ; Zuo *et al.*, 2020).

Basic Concepts of Herd Immunity

At the level of the individual, acquired immunity was build up either by immunization with a vaccine or natural infection with a pathogen (Stephenson *et al* ., 2021). Herd immunity which is also defines as a resistance to the spread of an infectious disease within a population that is based on pre-existing immunity of a high proportion of individuals as a result of previous infection or vaccination, it arises from immunity of the individual, which in turn leads to a broader and more comprehensive immunity, which is the immunity of society (Wu *et al* ., 2020). This effect was often seen at the population level through programs of vaccination, that targets to activate the role of herd immunity, so that children under the age of vaccination and immunocompromised persons, who cannot be vaccinated, remain in a safe position from contracting the disease (Verity *et al* ., 2020), an accordance with this concept, the susceptible persons were gained indirect protection from infection, so the herd immunity has taken on its role in protection. In the simplest model, the

herd immunity threshold is based on a single parameter known as R0, or the basic reproductive number (Boyton and Altmann, 2021). R0 indicates the average number of secondary infections caused by a single infectious individual introduced into a population that was fully susceptible to infection. (Kissler *et al* ., 2020 ; Nasiri *et al* ., 2020). If we consider a hypothetical pathogen with an R0 of 4, this means that, on average, one infected host will infect four others during the infectious period, assuming no immunity exists in the population. Therefore, the more communicable a pathogen, the greater it's associated R0 and the greater the proportion of the population that must be immune to block sustained transmission (Liu *et al.*, 2020). A similar parameter important for understanding population-level immunity is the effective reproduction number (Re or Rt). Re is defined as the average number of secondary cases generated by a single index case over an infectious period in a partially immune population (Aschwanden, 2021). Unlike R0, Re does not assumed a completely susceptible population and, consequently, will vary depending on a population's current immune state, which will change dynamically as an outbreak event or vaccination campaign unfolds (Fantanet and Cauchemes, 2020). The target of vaccination programs is to raise the Re value below 1. This occurs when the proportion of the immune population exceeds the herd immunity threshold. At this stage, the spread of the pathogen cannot be maintained, so there was a decrease in the number of infected individuals in the population (Randolph and Barreiro, 2020).

COVID-19 cases with bacterial co-infections

Bacterial co-infections are demonstrated in viral respiratory tract infections, which represent huge concern leading to disease and death (Wilson *et al* ., 1996 ; Rynda-Apple *et al.*, 2015). The microbial infections associated with COVID- 19, whether viral, bacterial or fungal, were considered medically important because they made it difficult to diagnose, identify and treat the infection and may lead to other diseases that constitute a double burden on the health of the infected person (Huang *et al* ., 2020 ; Page *et al* ., 2021). The most important causes of concomitant infection is the presence of bacteria and its endemicity in the atmosphere of hospitals and its acquisition of antibiotics resistance, which increased its virulence and thus became predisposed to infecting immunocompromised patients (Zu *et al.*, 2020). A viral dynamics, collection of clinical samples, route of transmission, adequate pathways to prevent disease spread, and effective pharmacological therapies, remain unclear (Paget and Trottein, 2019).

Antibiotics were still prescribed for treatment cases infected with COVID-19, while they ineffective for treatment of viral infections (Wu and McGoogan, 2020).

There are many reasons for doing this, it includes the difficulty of excluding bacterial co-infection during the disease as well as the ability of re-infection with bacteria again during the disease period (McCuller, 2014).

Rates of bacterial co-infection were increased in patients admitted to intensive care units, and these diseases could be due to super-infection by antibiotic-resistant bacteria in hospitals (Samaneh *et al.*, 2022). In this situation, the urgent need arises to review frequent and experimental prescribing of broad-spectrum antibiotics for patients with COVID-19 (Paget and Trottein, 2019).

According to many articles have shown that influenza viruses can be associated with secondary bacterial pneumonia that may occur during hospital admission, then developed complications that may lead to death in patients with or without pre-existing respiratory diseases (Chen *et al.*, 2020 ; WHO, 2020). On the other hand, viral infections can give way to bacterial infections, encouraging them, as in respiratory syncytial virus infection to respiratory passages (Arunachalam *et al.*, 2020), the damage of ciliated cells result in deterioration of muco-ciliary clearance by the virus which can increased adhesion of bacteria to mucins, then enhanced colonization of the bacteria in the airway (You *et al.*, 2017). After an acute inflammatory reaction and lungs tissue damage caused by a viral infection, a repair phase of lungs tissue occured, and because of the diverse immune responses in different individuals, this stage may lead to increase susceptibility to bacterial respiratory infections, so new bacterial adhesion receptors can emerged after virus-induced death of airway epithelial cells (Lai *et al.*, 2020). Thus, after viral infection, bacterial super infection can occur which in turn may lead to increased morbidity and mortality rates (Metlay *et al.*, 2019). Secondary infections may significantly reduces the survival of COVID-19 patients, and may be lead to another types of co-infection (Lai *et al.*, 2020), as fungal co-infections as well as viral co-infections that include commonest co-pathogen, *Candida glabrata*, *Candida albicans*, influenza A rhinovirus respectively (Arabi *et al.*, 2017). In addition, there was another group of viruses that have been identified as co-pathogens, such as influenza B virus, parainfluenza, metapneumovirus, coronavirus, and respiratory syncytial virus (Alfaraj *et al.*, 2017 ; Metlay *et al.*, 2019).

Mechanism of bacterial co-infections

The bacterial co-infection was arised from hospital-associated bacteria that invade hospitals airspace and adapted to develop an infection in individuals with a weakened immune system (Bengoechea and Bamford, 2020). Viral respiratory system

infections were accompanied by opportunistic bacteria or nosocomial infections, leading to secondary bacterial infections (Arunachalam *et al.*, 2020).

After The COVID-19 got entrance to human cells via adhesion to ACE2 protein-specific receptor of the cells that lining the upper and lower respiratory system (ven-Bekel *et al.*, 2020). Virus begin to make pathological changes in lungs tissues nature, include induction of airway damage, goblet cell hyperplasia, losing of cells, reduction in frequency of ciliary beat, altered mucus secretion, decreased in oxygen exchange, finally, breakdown of immune defenses (Seymour *et al.*, 2020). All these changes in the composition of the tissues of the respiratory cells gave an opportunity for pathogenic bacteria and even the normal flora to increase adherence and invasion to infected lungs tissues (Seymour *et al.*, 2020 ; Tay *et al.*, 2020).

The high levels of pro-inflammatory cytokines might lead to shock, respiratory failure or multiple organ failure (Alhazzani *et al.*, 2020). After an acute inflammatory reaction that lead to damage in lungs tissue caused by infection of virus, all of this may increase susceptibility to bacterial respiratory infections (Arunachalam *et al.*, 2020).

Antibiotics ineffective for infection with COVID-19, but it prescribed to individuals who suspected or documented COVID-19 infection because of the possibility of secondary bacterial infection during the course of the disease (Giamarellos-Bourboulis *et al.*, 2020), and to reduce the risk of death for COVID-19 patients with super-infection during influenza epidemics, many guidelines call for the use of empirical antibiotics for patients with severe COVID-19 (Karla *et al.*, 2020 ; Nuovo *et al.*, 2020).

Antimicrobial treatment should be used as soon as possible, with a guarantee of its effectiveness against infection (WHO, 2019 ; Prompetchara *et al.*, 2020). It is important to do culture and antibiotics susceptibility test for patients to identify the concerned bacteria (Weston *et al.*, 2020), and then determine the appropriate treatment or antibiotics, rather than keeping the patient in a state of double treatment for a long time (Sultani *et al.*, 2021). The sudden epidemic caused by COVID- 19 affected people all over the world, and with its emergence and spread, an urgent necessity arose to find a vaccine against the virus, or to discover or develop modern antivirals (Moreno-Garcia *et al.*, 2022).

Conclusions

1. Both innate and adaptive immune responses were stimulated against this virus in patients infected with COVID-19. All types of immune cells participated in the defense against the virus, but the immune response of patients varies depending on the efficiency and strength of their immune system.
2. The elderly and immune-compromised individuals were more affected than others, due to the weakening of their immune system, so death rates are high among them.
3. Bacterial infections occur accompanying patients infected with COVID- 19 and were often acquired from the atmosphere of hospitals and intensive care units, and the weakened immune system of those infected individuals helped to increase the acquisition of these bacterial infections.
4. Bacterial co-infections associated with COVID-19 may lead to high mortality rates among patients.
5. Herd immunity can be reached through community members receiving available and specialized vaccines that work against COVID- 19.

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