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Review article

Interplay between Bacterial Infections and COVID-19: Mechanisms, Implications, and Management

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ABSTRACT

The COVID-19 pandemic is one of the biggest changes humanity has faced over many centuries, causing health, social and economic disasters. Bacterial co-infections with COVID-19, especially respiratory tract bacteria play an important role in increasing the severity of the epidemic, increasing the mortality and morbidity rate, especially among elderly patients and immunosuppressive patients. Infection with the COVID-19 virus paves the way for the occurrence of high-risk bacterial respiratory infections caused by many species, through the effect of this virus on the immune system and the destruction of lung tissue. Immune modulation is considered one of the strategies that the body follows to confront COVID-19 infection and co-bacterial infections. That may cause affect negatively on the human body as a result of immunosuppression due to many factors, including the use of immunosuppressive drugs. The mechanism of interaction between infection with COVID-19 and co-bacterial infection is governed by several factors, including the role of the virus in paving the way for the infection to occur, in relation to its effect on the immune system directly or indirectly, in addition to the role of the virus in removing barriers to bacteria to cause infection. The use of antibiotics in an appropriate manner (not excessive) can have a positive impact on the treatment of bacterial infections associated with infection with COVID-19, as well as vaccination against some respiratory system bacteria, in addition to COVID-19. The trend in the future is to innovate ways to treat or vaccinate the cases of suffering from COVID-19 co-bacterial infections could play an important role in reducing the death rate in these cases.

Keywords: Bacterial infection, COVID-19, Immune response, Immunomodulation, Immunosuppression.

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1. INTRODUCTION

COVID-19 is a respiratory illness caused by a virus called SARS-CoV-2. It was first identified in Wuhan, China, in December 2019 and quickly spread around the world. COVID-19 is highly contagious and can cause a range of symptoms, from mild to severe [1]. The most common symptoms of COVID-19 are Fever, Cough, Shortness of breath, Fatigue, Muscle aches, Headache, Sore throat, Loss of taste or smell, Congestion or runny nose, Nausea or vomiting, and Diarrhea. Some people with COVID-19 may develop more serious complications, such as pneumonia, acute respiratory distress syndrome (ARDS), and multisystem inflammatory syndrome in children (MIS-C). COVID-19 is spread primarily through respiratory droplets produced when an infected person coughs or sneezes. These droplets can land in the mouths or noses of

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people who are nearby or possibly be inhaled into the lungs. COVID-19 can also be spread through contact with contaminated surfaces or objects. There is no specific treatment for COVID-19, but most people recover with supportive care. Some people with severe COVID-19 may need to be hospitalized and treated with supplemental oxygen, mechanical ventilation, or other supportive measures [2]. The interaction between respiratory tract bacterial infections and COVID-19 is complex and still being studied. COVID-19 can make bacterial infections more likely. COVID-19 can damage the lungs and make them more susceptible to bacterial infection. This is because COVID-19 can damage the cells that line the airways and make it easier for bacteria to enter the lungs. Additionally, COVID-19 can weaken the immune system, making it more difficult for the body to fight off bacterial infections. Bacterial infections can make COVID-19 worse. COVID-19 can damage the immune system and make it more difficult for the body to fight off bacterial infections. Additionally, COVID-19 can increase the risk of developing certain types of bacterial infections, such as pneumonia and sepsis [3]. Bacterial infections can be more common in people with COVID-19. Studies have shown that people with COVID-19 are more likely to develop bacterial infections, especially pneumonia. This is likely due to the damage that COVID-19 does to the lungs and the immune system. Bacterial infections can complicate the treatment of COVID-19. People with COVID-19 who develop bacterial infections may need to be hospitalized and treated with antibiotics [1]. This can complicate the treatment of COVID-19 and make it more difficult for people to recover. Researchers are still working to understand the full extent of the relationship between bacterial infections and COVID-19. However, it is clear that the two conditions above can interact with each other in a number of ways and that it is important to be aware of the potential risks.

2. BACTERIAL INFECTION AND IMMUNITY

The human immune response to bacterial infections is a complex and coordinated defense mechanism that aims to identify, neutralize, and eliminate invading bacteria. The immune response can be divided into two main components: the innate immune system and the adaptive immune system. These two systems work together to combat bacterial infections.

2.1. Innate Immune Response

The first line of defense includes physical barriers such as the skin and mucous membranes, which prevent bacteria from entering the body. Additionally, various antimicrobial substances like lysozymes and acidic environments help kill or inhibit the growth of bacteria. When bacteria breach these barriers, cells of the innate immune system, such as neutrophils and macrophages, engulf and digest them through a process called phagocytosis. These cells recognize bacteria through pattern recognition receptors (PRRs) that detect specific molecular patterns on the bacterial surface. In response to infection, the body releases inflammatory mediators like histamines and cytokines. These substances promote vasodilation, increased blood flow to the infected area, and recruitment of immune cells, further enhancing the body's ability to combat the infection [4].

2.2. Adaptive Immune Response

Macrophages and dendritic cells present bacterial antigens (pieces of bacteria) to T cells and B cells. This process activates specific immune responses against the infecting bacteria. T cells play a crucial role in the adaptive immune response. Cytotoxic T cells directly attack and destroy infected host cells, while helper T cells stimulate other immune cells and promote the production of antibodies. The adaptive immune response is divided into two branches, Humoral Immunity (B cells), the B cells differentiate into plasma cells, which produce antibodies (Immunoglobulins) specific to the bacteria. Antibodies help neutralize bacteria and promote their removal by phagocytic cells. While, the memory Response happens after the infection is resolved, where, some immune cells, known as memory cells, remain in the body. They provide long-term immunity by recognizing and responding more rapidly to the same bacterial pathogen if it re-infects the host in the future. The immune response to bacterial infections can vary depending on the type of bacteria, their virulence factors, and the host's immune system. Some bacteria may evade or subvert the immune response, leading to chronic or recurrent infections [5]. Vaccination is a preventive measure that stimulates the adaptive immune system to produce antibodies and memory cells without causing disease, thus preparing the body to mount a rapid and effective response if exposed to the pathogen in the future [6]. In severe cases, when the immune response is overwhelmed or dysregulated, it can lead to conditions like sepsis, where the body's inflammatory response becomes excessive and harmful [7]. Proper medical treatment, such as antibiotics, may be necessary to supplement the immune response and combat bacterial infections effectively.

3. COVID-19 INFECTION AND IMMUNE SYSTEM ABILITY TO COMBAT BACTERIA

Viral infections, including COVID-19, can have a significant impact on the immune system's ability to combat bacteria [8]. This can occur due to the diversion of Immune Resources, during a viral infection, the immune system primarily focuses on combating the virus. Immune cells like T cells and B cells are activated to target and eliminate virus-infected cells. This diversion of resources and attention away from bacterial threats can weaken the immune response against bacteria [9]. Prolonged or severe viral infections can lead to immune exhaustion, where immune cells become less responsive and less effective. This exhaustion can impair the immune system's ability to mount an effective response against bacterial co-infections. Viral infections can weaken the body's defenses, making it more susceptible to bacterial infections [8]. For example, individuals with severe viral pneumonia, such as COVID-19, may be at increased risk of developing secondary bacterial pneumonia. This is often due to damaged lung tissues, impaired mucociliary clearance, and weakened immune responses in the respiratory tract [10]. Certain viral infections can induce immunosuppression. For instance, the human immunodeficiency virus (HIV) specifically targets and impairs the immune system, making individuals more susceptible to bacterial infections [11]. While COVID-19 primarily affects the respiratory system, severe cases can also lead to systemic inflammation and immune dysfunction. In the case of COVID-19, many patients with severe symptoms are administered antibiotics as a precautionary measure to prevent or treat bacterial co-infections. However, unnecessary or improper use of antibiotics can lead to antibiotic resistance and disrupt the balance of the microbiome, potentially weakening the immune system's ability to combat bacteria. It's important to note that not all viral infections have the same impact on the immune system's response to bacteria [12]. The extent to which viral

infections affect bacterial susceptibility depends on various factors, including the specific virus, the severity of the infection, the individual's overall health, and any underlying medical conditions. In the context of COVID-19, healthcare providers often monitor patients closely for bacterial co-infections and administer antibiotics when necessary. This is particularly important in severe cases where the respiratory system is compromised. Additionally, vaccination against preventable bacterial infections (e.g., pneumococcal) and influenza vaccines are recommended to reduce the risk of co-infections during a viral pandemic like COVID-19. Overall, maintaining a healthy immune system through vaccination, good hygiene practices, and appropriate medical care is essential to minimize the risk of bacterial co-infections during viral illnesses [13].

4. IMMUNOMODULATION IN CONTEXT OF VIRAL AND BACTERIAL CO-INFECTIONS

Immunomodulation is the process of altering the immune system to achieve a desired outcome. This can be done through a variety of methods, including drugs, vaccines, and lifestyle changes. In the context of viral and bacterial co-infections, immunomodulation can be used to reduce the severity of the infection, prevent the development of complications, and promote recovery [14]. Immunomodulation can also be used to improve the efficacy of antibiotic treatment. There are a number of different immunomodulatory therapies that can be used to treat viral and bacterial co-infections. Some of the most common therapies include such as antibiotics are used to kill bacteria. They can also be used to treat viral infections that are complicated by bacterial infections, and antivirals are used to treat viral infections. They work by inhibiting the replication of the virus [15].

Immunomodulation can be done by Immunosuppressants are used to suppress the immune system. This can be helpful in cases where the immune system is overreacting and causing damage to the body [16]. Immunomodulation can be done by Immunostimulants which are used to stimulate the immune system [17]. This can be helpful in cases where the immune system is not responding strongly enough to the infection. The best immunomodulatory therapy for a particular viral and bacterial co-infection will depend on the type of viruses and bacteria involved, the severity of the infection, and the patient's individual health status. There are some examples of how immunomodulation can be used to treat viral and bacterial co-infections: i, A person with HIV/AIDS may be given antibiotics to prevent bacterial infections. ii, A person with influenza may be given an antiviral medication to reduce the severity of the infection and prevent complications. iii, A person with cystic fibrosis may be given an immunostimulant to help their body fight off bacterial infections [18]. iv, A person with a severe bacterial infection may be given an immunosuppressant to reduce inflammation and prevent damage to the body. Immunomodulation is a complex and rapidly evolving field. Researchers are constantly developing new and more effective immunomodulatory therapies. It is important to note that immunemodulation can have both positive and negative side effects. It is important to talk to your doctor about the risks and benefits of immunomodulation before starting any treatment [19].

5. BACTERIAL CO-INFECTIONS IN COVID-19 Patients

Specific species of bacterial co-pathogens were reported in 11/24 studies (45.8%), representing less than 14% of patients with reported infections. The most common organisms reported were *Mycoplasma* species (n = 11 patients, n = 3 reported as *M. pneumoniae*), *Haemophilus influenzae* (n = 5 patients), and *Pseudomonas aeruginosa* (n = 5 patients) [20]. The prevalence of bacterial co-infections among COVID-19 patients can vary depending on several factors, including the geographic region, the population studied, and the severity of the COVID-19 cases. Bacterial co-infections among COVID-19 patients were generally reported to be relatively low. Studies conducted during the early stages of the COVID-19 pandemic suggested that the majority of COVID-19 cases were caused by the SARS-CoV-2 virus alone, without a concurrent bacterial infection. Bacterial co-infections were more commonly observed in severe or critically ill COVID-19 patients. Pneumonia, often caused by bacteria such as *Streptococcus pneumoniae* or Staphylococcus aureus, was one of the most frequently reported bacterial co-infections in severe COVID-19 cases. The prevalence of bacterial co-infections varied by geographic region. In some areas, bacterial co-infections were more common than in others. This could be influenced by factors such as local healthcare practices, antibiotic use, and the prevalence of certain bacterial pathogens in the community. Streptococcus pneumoniae (the bacterium responsible for many cases of pneumonia) was frequently mentioned in studies as a potential bacterial co-infection in COVID-19 patients, particularly in severe cases with respiratory symptoms [21, 22]

Certain risk factors and patient populations may be more susceptible to bacterial co-infections in COVID-19 patients. Bacterial co-infections are more likely to occur in individuals with specific predisposing factors or conditions. Bacterial co-infections are more commonly observed in severe or critically ill COVID-19 patients. Patients with severe respiratory symptoms, acute respiratory distress syndrome (ARDS), or those requiring mechanical ventilation are at greater risk. Severe lung damage from COVID-19 can compromise the body's defense mechanisms against bacterial pathogens. Elderly individuals, especially those over 65, are more susceptible to both severe COVID-19 and bacterial co-infections [23].

Aging is often associated with a weakened immune system, making older adults more vulnerable to infections. Individuals with underlying health conditions, such as diabetes, heart disease, chronic respiratory diseases (e.g., COPD), or immunosuppressive conditions, are at higher risk of bacterial co-infections. These conditions can impair the body's ability to fight off infections. Patients who are immunocompromised due to factors like cancer treatment, organ transplantation, or certain medications (e.g., corticosteroids) have a weakened immune system, making them more susceptible to bacterial co-infections [24]. Individuals with pre-existing respiratory tract infections, such as chronic bronchitis or bronchiectasis, may be more prone to bacterial co-infections in the respiratory system when they contract COVID-19. Patients who have recently taken antibiotics for other reasons may be at a higher risk of bacterial co-infections, as antibiotic use can disrupt the balance of the microbiome and create conditions favorable for bacterial growth. Being hospitalized for COVID-19, especially in intensive care units (ICUs), increases the risk of hospital-acquired bacterial infections, such as ventilator-associated pneumonia or bloodstream infections. Prolonged hospital stays can increase the risk of acquiring bacterial infections due to exposure to healthcare-associated pathogens [25].

The use of invasive medical procedures, such as intubation and mechanical ventilation, central lines, and urinary catheters, can introduce bacteria into the body and increase the risk of secondary bacterial infections. In cases where COVID-19

coincides with influenza infections (flu), the risk of bacterial co-infections may be higher due to the dual viral assault on the respiratory system. It's essential for healthcare providers to consider these risk factors when assessing and managing COVID-19 patients. Timely diagnosis and appropriate treatment with antibiotics are crucial if bacterial co-infections are suspected or confirmed [26].

6. MECHANISMS OF INTERATION

COVID-19 can predispose individuals to bacterial infections through several mechanisms, primarily related to the impact of the virus on the respiratory system and the immune response in the following ways: i, Respiratory Damage: COVID-19 primarily targets the respiratory system, causing inflammation and damage to lung tissue. This damage can impair the normal mechanisms that protect the airways from bacterial colonization and infection. Injured lung tissue can become a breeding ground for bacteria, making bacterial infections, particularly pneumonia, more likely [27]. ii, Weakened Mucociliary Clearance**:** The respiratory tract is lined with tiny hair-like structures called cilia and is covered in a layer of mucus that helps trap and remove foreign particles, including bacteria. COVID-19 can disrupt this mucociliary clearance mechanism, allowing bacteria to persist and potentially cause infections in the respiratory tract [28]. iii, Altered Immune Response: COVID-19 can lead to immune dysregulation and a cytokine storm, where the immune system overreacts and releases excessive inflammatory cytokines. This inflammatory response can weaken the immune system's ability to combat bacterial infections effectively. It may also compromise the integrity of the respiratory epithelium, providing bacteria easier access to lung tissue [29]. iv, Immunosuppressive Treatments: Some COVID-19 patients, especially those with severe cases, may receive immunosuppressive treatments like corticosteroids or other immune-modulating drugs to manage the hyperinflammatory response. While these treatments are essential for managing severe COVID-19, they can suppress the immune system, making patients more vulnerable to bacterial infections. v, Invasive Medical Procedures: Patients with severe COVID-19 may require invasive medical procedures, such as intubation and mechanical ventilation, central venous catheter placement, or urinary catheterization. These procedures can introduce bacteria into the body and increase the risk of hospital-acquired bacterial infections. vi, Hospitalization**:** Hospitalized COVID-19 patients, especially those in intensive care units (ICUs), are at an increased risk of acquiring bacterial infections due to prolonged hospital stays, close contact with healthcare workers, and exposure to healthcare-associated pathogens [26]. vii, Secondary Infections: In some cases, COVID-19 can weaken the immune system and create conditions favorable for opportunistic bacterial infections. Bacteria that are normally harmless or present in low numbers in the respiratory tract can become pathogenic in the context of COVID-19. viii, Use of Antibiotics: In the effort to manage COVID-19, some patients may receive antibiotics as a precautionary measure to prevent or treat bacterial co-infections. While antibiotics can be essential when bacterial infections are suspected, their indiscriminate use can contribute to antibiotic resistance and the development of superbugs [15]. ix, Co-Infections: Patients with COVID-19 can also develop bacterial co-infections, particularly in the respiratory tract. Co-infections can exacerbate the severity of illness and complicate the clinical course. It's essential for healthcare providers to be vigilant for signs of bacterial infections in COVID-19 patients, especially those with risk factors such as severe disease, prolonged hospitalization, or immunosuppressive treatments. Timely diagnosis and appropriate antibiotic therapy are critical to managing bacterial co-infections and reducing associated morbidity and mortality.

6.1. Cytokine Storm

A cytokine storm is an excessive and dysregulated immune response characterized by the release of large amounts of pro-inflammatory cytokines. In the context of COVID-19, a cytokine storm is often associated with severe disease. Cytokine storms can have a detrimental effect on the immune system's ability to combat bacterial co-infections. The overwhelming inflammation and activation of immune cells may divert resources away from fighting bacteria, impair the immune response, and weaken the host's defenses against secondary bacterial invaders [29, 30].

6.2. Immunosuppression

Severe COVID-19 cases, particularly those in which a cytokine storm occurs, may require treatments that suppress the immune response, such as corticosteroids or immunomodulatory drugs. These treatments are used to control the excessive inflammation seen in severe cases. The immunosuppressive treatments are essential in managing severe COVID-19, they can increase the risk of bacterial co-infections. Immunosuppression weakens the patient's immune defenses, making it easier for bacteria to proliferate and cause infections. Therefore, a delicate balance must be maintained between controlling the hyperinflammatory response and preserving the ability to combat bacterial pathogens [31].

6.3. Respiratory Damage

COVID-19 often causes lung damage, including inflammation, fluid accumulation, and tissue injury in the respiratory tract. This damage can affect the function of the lungs and impair the body's ability to clear infections. Respiratory damage can make COVID-19 patients more susceptible to bacterial co-infections, particularly pneumonia. The damaged lung tissue provides a favorable environment for bacterial colonization and growth. Additionally, compromised lung function can impair the body's ability to clear bacteria from the respiratory tract, increasing the risk of secondary bacterial infections [32].

The interaction between these factors is complex and can vary from patient to patient. In some cases, the hyperinflammatory response seen in a cytokine storm can exacerbate lung damage and increase susceptibility to bacterial co-infections. In others, immunosuppressive treatments may be necessary to control inflammation but can lead to immunosuppression and a higher risk of bacterial infections. Healthcare providers must carefully assess and manage COVID-19 patients, taking into account these factors. Timely diagnosis and appropriate treatment of bacterial co-infections, along with close monitoring of the patient's immune status and lung function, are crucial to achieving the best outcomes. Balancing the need to control inflammation with the risk of bacterial infections is a key challenge in the management of severe COVID-19 cases [30].

6.4. Future Directions and Research Gaps

Further research is needed to better understand the relationship between bacterial infections and COVID-19 in a number of areas, including the mechanisms by which COVID-19 increases the risk of bacterial infection. We know that COVID-19 can damage the lungs and weaken the immune system, but more

research is needed to understand how these changes lead to an increased risk of bacterial infection. The impact of bacterial co-infection on the severity and outcome of COVID-19 [33]. Studies have shown that bacterial co-infection is associated with worse outcomes in COVID-19 patients, but more research is needed to understand the full impact of bacterial co-infection on COVID-19 prognosis. The best ways to prevent and treat bacterial co-infection in COVID-19 patients. There is currently no consensus on the best way to prevent and treat bacterial co-infection in COVID-19 patients. More research is needed to develop evidence-based guidelines for the prevention and treatment of bacterial co-infection in this population.

7. CONCLUSION

Bacterial infections that occur as a result of infection with the Covid-19 virus are considered serious cases that can contribute to increasing the mortality and morbidity that associated with COVID-19 infection especially in people who suffering from immune suppressive disease or elder persons. Treating bacterial infections associated with COVID-19 using antibiotics is one of the recommended methods. Immune modulation can contribute to reducing the severity of these conditions. In addition, the most promising strategy for reducing the risk of infection with COVID-19 is vaccinating people, especially the elderly, against widespread types of bacteria that cause pneumonia and also getting COVID-19 vaccine.

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Conflict of interest

The authors declare that they have no conflict of interests.

Ethical Approval

This review was approved by the Ethical Committee of the Ministry of Health, Baghdad, Iraq (No 243, 2021).

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