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Review Article

Multiple microbial coinfections occurred during COVID-19 pandemic

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ABSTRACT

The COVID-19 pandemic brought to light a complex challenge: the occurrence of multiple microbial co-infections in affected individuals. In addition to the primary infection caused by the SARS-CoV-2 virus, patients often had to contend with secondary infections caused by bacteria, viruses, and fungi. This complicated interaction of pathogens has presented significant clinical, diagnostic, and therapeutic hurdles. It has been observed that co-infections can exacerbate disease severity and complicate treatment strategies, necessitating a more comprehensive approach to patient care. In addition, distinguishing between viral and bacterial/fungal coinfections based on clinical symptoms alone remains a difficult task, underscoring the need for advanced diagnostic tools. The emergence of coinfections has also heightened concerns about antimicrobial resistance due to the widespread use of antibiotics and antifungals, underscoring the importance of prudent antimicrobial stewardship. As the pandemic continues to evolve, understanding, diagnosing, and effectively managing these multiple microbial coinfections have become critical imperatives for healthcare systems and researchers worldwide. The present review illustrated the past occurrence of various microbial infections that co-existed with the COVID-19.

1. Introduction

The novel coronavirus SARS-CoV-2 that triggered the COVID -19 pandemic has posed unprecedented challenges to health systems and societies around the world. Much work has been done to understand the virology, epidemiology, and clinical management of COVID -19. However, microbial coinfections in people with COVID -19 are becoming an emerging area of concern. Microbial coinfections occur when COVID -19 patients have concurrent SARS-CoV-2 and other infectious agents such as bacteria, viruses, or fungi.[1–3] This combination of microbes could complicate the clinical course of COVID -19, making it more difficult to diagnose, treat, and predict the course of the disease. Bacterial co-infections, especially secondary bacterial pneumonia, are a major problem in COVID -19, especially in people who are sick enough to require hospitalization. There are reports that pathogens such as *Streptococcus pneumoniae*, *Staphylococcus aureus*, and *Haemophilus influenzae* are often responsible.[4] These bacterial co-infections can worsen respiratory symptoms, cause more damage to the lungs, and increase the risk of death. Overuse of antibiotics to treat suspected co-infections has also led to concerns about drug resistance and damage to microbial ecosystems. In addition to bacterial coinfections, SARS-CoV-2 and other respiratory viruses such as influenza and Respiratory Syncytial Virus (RSV) have been shown to interact, complicating diagnosis and

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treatment. Invasive fungal co-infections such as invasive *aspergillosis* and *candidiasis* have been observed, mostly in COVID -19 patients with severe disease who require mechanical ventilation and immunosuppressive treatment.[5] Another association with COVID-19 immunosuppression is reactivation of latent infections, especially tuberculosis (TB). When TB and COVID -19 occur together, they pose a dual public health threat and must be diagnosed and treated differently. This thorough study addresses the many other aspects of microbial coinfections in COVID-19, including their prevalence, clinical symptoms, diagnostic strategies, treatment challenges, and impact on patient care.[6,7] It also highlights the importance of keeping track of people, using antibiotics judiciously, vaccinating them, and conducting further studies to find out how SARS-CoV-2 and other pathogens interact. This will help us understand the clinical complexity of COVID -19 and improve patient outcomes.

2. Bacterial Co-infection

Bacterial co-pathogens are typical of viral respiratory infections, such as influenza. They are also an important cause of morbidity and mortality, requiring rapid diagnosis and treatment with antibacterial drugs.[8] Bacterial co-infection has been found to be as high as 20–30% in patients with severe influenza and is associated with higher severity of illness, greater utilisation of healthcare resources, and increased risk of mortality. However, the prevalence of bacterial coinfection in patients with severe influenza varies widely from study to study. It has been identified as a major knowledge gap because the prevalence, incidence, and characteristics of bacterial infection in persons infected with Severe Acute Respiratory Syndrome Coronavirus 2 (SARS-CoV-2) have not been well studied.[9]

The COVID-19 pandemic has presented an unprecedented challenge to health care providers worldwide. Health care workers have had to deal with the complexity of the co-infections, especially bacterial co-infections, in COVID -19 patients. This is in addition to the primary viral infection caused by the new coronavirus SARS-CoV-2. One of the biggest concerns with bacterial co-infections during COVID -19 is that they exacerbate respiratory problems. Bacterial germs such as *Escherichia coli*, *Haemophilus influenza*, *Klebsiella pneumonia*, *Legionella pneumophila*, *Pseudomonas aeruginosa*, *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Mycobacterium tuberculosis* can invade damaged lung tissue and cause secondary bacterial *pneumonia*.[8–11] There are several others that greatly affect the situation during the pandemic (Table 1A). This can exacerbate respiratory problems and increase the likelihood that something bad will happen. It can be difficult to distinguish between viral and bacterial illnesses based on their symptoms alone, as both can cause fever, cough, and shortness of breath.[12] Because of the difficulty in making a diagnosis, antibiotics are often given on a whim, even if there is no clear evidence of bacterial infection. Studies have shown that COVID -19 patients with bacterial co-infections have a higher risk of disease and death. Secondary bacterial *pneumonia* or bloodstream disease can cause a patient to stay in the hospital longer and increase the likelihood that something bad will happen.[13]

Coinfections between tuberculosis (TB) and COVID -19 have been detected in areas where both diseases are common. These coinfections can complicate the treatment of affected individuals and complicate the clinical course for patients. COVID -19 has been associated with reactivation of latent TB infection in regions with a high burden of tuberculosis TB, such as parts of sub-Saharan Africa and South Asia. Latent tuberculosis occurs when TB bacteria (*Mycobacterium tuberculosis*) are present in the bodies of people who do not have active disease. Latent tuberculosis (TB) can become active again after immunosuppression caused by COVID -19. Because both TB and COVID -19 affect the respiratory system, individuals who have them at the same time are at higher risk for serious illness and its consequences.[6] These patients may require hospitalization and oxygen therapy as part of their treatment. Individuals with TB and COVID -19 co-infections may be difficult to treat. Simultaneous treatment of multiple diseases may require changing treatment plans, watching for drug interactions, and considering how COVID -19 medications might affect TB treatment. It is worth noting that COVID -19 TB coinfection rates and clinical relevance may vary by group and geographic location.

3. Fungal Co-infection

Patients with coronavirus infection 2019 (COVID -19) often suffer from fungal co-infections, which can worsen clinical outcomes and complicate treatment. Despite this, research into fungal co-infections in this population has been limited. The most common fungal infections associated with COVID -19 are *candidiasis*, *aspergillosis*, and *mucormycosis*, and they all have a significant impact on mortality rates.[14,15] Treatments for COVID -19 (such as steroids and other medications) can impair the body's defences against fungi; therefore, it is likely that COVID -19 increases the risk for fungal infections. *Aspergillosis*, invasive *candidiasis*, and *mucormycosis* (often incorrectly referred to as "black fungus") are the most commonly reported fungal infections in persons with COVID -19.[16–18] Fungal infections resistant to antifungal therapy have also been reported in patients with severe COVID -19. Extreme cases of COVID -19 have not been extensively studied for *aspergillosis* (infections caused by the fungus *Aspergillus*).[17] In the past, physicians assumed that only people with weakened immune systems were susceptible to *aspergillosis*.

Table 1: List of multiple microbial co-infection during COVID-19.

Bacterial infection and behaviour with COVID-19 (A)		
Streptococcus pneumonia Infection	*Streptococcus pneumoniae*, often referred to as pneumococcus, is a common cause of bacterial *pneumonia*. It can co-infect COVID -19 patients and cause severe respiratory symptoms.	Root-Bernstein, 2021 [19]
Staphylococcus aureus Infection	*Staphylococcus aureus*, including methicillin-resistant *Staphylococcus aureus* (MRSA), can cause secondary bacterial *pneumonia* in COVID -19 patients. MRSA infections are particularly difficult to treat due to antibiotic resistance.	Tsai [20] et al., 2023
Haemophilus influenza Infection	*Haemophilus influenzae* can cause respiratory infections and *pneumonia*. Coinfection with this bacterium can complicate the clinical course of COVID -19.	Lansbury [10] et al., 2020
Klebsiella pneumonia Infection	*Klebsiella pneumoniae* is another bacterium that can cause secondary *pneumonia* in COVID -19 patients, especially in hospitals.	García-Meniño [21] et al., 2021
Escherichia coli Infection	*Escherichia coli* infections can manifest as urinary tract infections, bloodstream infections, and respiratory tract infections. Co-infections with E. coli have been reported in COVID -19 cases.	Basnet [11] et al., 2022
Legionella pneumophila Infection	*Legionella pneumophila* is associated with Legionnaires' disease, a severe form of *pneumonia*. Coinfection with Legionella has been documented in COVID -19 patients.	Chaudhary [22] et al., 2020
Pseudomonas aeruginosa Infection	*Pseudomonas aeruginosa* is an opportunistic pathogen that can cause a number of infections, including respiratory tract infections. Co-infections with *Pseudomonas* have been reported in individuals with severe COVID -19.	Mahmoudi [7] , 2020
Group A *Streptococcus (Streptococcus pyogenes*) Infection	Group A *Streptococcus* can cause a variety of infections, including strep throat and invasive disease such as necrotizing fasciitis. Co-infections with this bacterium have been documented in COVID -19 patients.	Efstratiou, [13] and Lamagni, 2022
Mycobacterium tuberculosis Infection	In areas of high tuberculosis burden (TB), reactivation of latent TB infection has been observed in some COVID -19 patients, resulting in TB co-infections.	Bandyopadhyay [6] et al., 2020
*Enterobacte*r spp. Infection	Several species of *Enterobacter* can cause infections, including respiratory and urinary tract infections. Coinfections with *Enterobacter* have been reported in addition to COVID -19.	Shafiekhani [23] et al., 2022
Fungal infection and behaviour with COVID-19 (B)		
Invasive *Aspergillosis*	*Aspergillus* species, particularly *Aspergillus fumigatus*, can cause invasive *aspergillosis* in COVID -19 patients, especially those who have undergone mechanical ventilation or immunosuppressive treatments.	El-Kholy, [16] El-Fattah and Khafagy, 2021
Candidiasis	*Candida* species such as *Candida albicans* can cause *candidiasis* in COVID -19 patients, including oral and systemic *candidiasis*. Prolonged use of broad-spectrum antibiotics and corticosteroids may predispose people to *candidiasis*.	Babamahmoodi [24] et al., 2022
Mucormycosis (Zygomycosis)	Mucormycetes are responsible for *mucormycosis*, a rare but serious fungal infection that can affect the sinuses, lungs, and other parts of the body. Cases of COVID -19-associated *mucormycosis*, often referred to as "black fungus," have been reported in some regions.	Pasrija [25] and Naime, 2022

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Table 1 continued

Pneumocystis *Pneumonia* (PCP)	*Pneumocystis jirovecii* is a fungus that can cause *pneumonia*, especially in persons with weakened immune systems. Although not common, cases of PCP have been reported in COVID -19 patients, especially those with severe disease.	Szydłowicz,[26] and Matos 2021
Coccidioidomycosis (Valley Fever)	*Coccidioides immitis* and *Coccidioides posadasii* are fungi responsible for coccidioidomycosis. In regions where this fungal infection is endemic, coinfections with COVID -19 have been reported.	Galgiani[27] et al., 2023
Cryptococcosis	*Cryptococcus neoformans* and *Cryptococcus gattii* can cause cryptococcosis, which primarily affects the lungs and central nervous system. Co-infections with *Cryptococcus* have been documented in some COVID -19 cases.	Lima[28] et al., 2021; Kassaza[29] et al., 2022;
Histoplasmosis	*Histoplasma capsulatum* is the fungus responsible for histoplasmosis, which primarily affects the lungs. Cases of histoplasmosis co-occurring with COVID-19 have been reported in areas where this fungal infection is endemic.	de Macedo[30] et al., 2021
Viral infection and behaviour with COVID-19 (C)		
Influenza (Flu) Co-Infection	Co-infection with influenza viruses (commonly influenza A or B) and SARS-CoV-2 has been reported in some cases. Co-infected individuals may experience more severe respiratory symptoms.	Kinoshita[31] et al., 2021
Respiratory Syncytial Virus (RSV) Co-Infection	RSV is another respiratory virus that can co-infect COVID-19 patients, leading to more severe respiratory symptoms and complications, especially in young children and the elderly.	Redondo[32] et al., 2023
Human Metapneumovirus (hMPV) Co-Infection	Human metapneumovirus is a respiratory virus that can cause symptoms similar to those of COVID-19. Co-infections with hMPV and SARS-CoV-2 have been documented.	Kozinska[33] et al., 2022
Rhinovirus Co-Infection	Rhinoviruses are a common cause of the common cold. Co-infection with rhinovirus and SARS-CoV-2 can lead to a combination of symptoms associated with both viruses.	Kasman[34] , 2022
Adenovirus Co-Infection	Adenoviruses can cause a range of respiratory and other infections. Co-infections with adenovirus and SARS-CoV-2 have been reported.	Root-Bernstein[8] , 2021, Root-Bernstein, 2023
Parainfluenza Virus Co-Infection	Parainfluenza viruses can cause respiratory infections, especially in children. Co-infections with parainfluenza viruses and SARS-CoV-2 can occur.	Tso[35] et al., 2022
Human Coronavirus Co-Infection	It's worth noting that other human coronaviruses (e.g., HCoV-OC43, HCoV-HKU1) that cause mild respiratory illnesses can co-circulate with SARS-CoV-2, potentially leading to co-infections.	Telenti[36] et al., 2021
Herpes Simplex Virus (HSV) Co-Infection	While less common, co-infections with herpes simplex virus, which can cause oral or genital herpes, have been documented in COVID-19 patients.	Franceschi[37] et al., 2022
Superinfections and behaviour with COVID-19 (D)		
Hospital-Acquired Pneumonia (HAP)	Hospital-acquired pneumonia is one of the most common superinfections in COVID -19 patients admitted to the hospital. Bacterial pathogens, including *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, and *Escherichia coli*, can cause HAP.	Karolyi[38] et al., 2022
Ventilator-Associated Pneumonia (VAP)	Ventilator-associated pneumonia is a form of HAP, which occurs in patients who are mechanically ventilated. It is often caused by bacteria such as *Staphylococcus aureus* and *Enterobacter species*.	Saied et al., 2019

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Table 1 continued

Central Line-Associated Bloodstream Infections (CLABSI)	COVID-19 patients who require central venous catheters or other invasive devices are at risk of developing CLABSI, which can be caused by bacteria such as *Staphylococcus aureus* and Enterococcus species.	Goel[39] et al., 2022
Catheter-Associated Urinary Tract Infections (CAUTI)	People with COVID -19 who wear urinary catheters may develop CAUTI, which are often caused by *Escherichia coli* and Enterococcus species.	Chadha[40] et al., 2023
Surgical Site Infections (SSI)	COVID-19 patients undergoing surgery are at risk for SSI, which can be caused by a variety of bacteria, including *Staphylococcus aureus*.	Habib[41] et al., 2022
Clostridium difficile Infection	*Clostridium difficile* infection may occur as a superinfection in individuals who have had prolonged antibiotic therapy, which is common in the treatment of COVID-19. This infection leads to severe diarrhea and colitis.	Duhan[42] , Keisham, and Salim, 2023
Candidiasis	*Candida* species can cause secondary infections in COVID-19 patients, particularly those receiving prolonged courses of broad-spectrum antibiotics or immunosuppressive treatments.	Nambiar[43] et al., 2021
Multidrug-Resistant Infections	In healthcare settings with high antibiotic use, superinfections with multidrug-resistant bacteria, such as methicillin-resistant *Staphylococcus aureus* (MRSA) or carbapenem-resistant Enterobacteriaceae (CRE), are of concern.	Ramos[44] et al., 2021
Antibiotic Use and Behaviour with COVID-19 (E)		
Diagnostic Challenges	Distinguishing between viral and bacterial infections based solely on clinical symptoms can be challenging. Therefore, diagnostic tests such as sputum cultures, blood cultures, urine cultures, and imaging studies may be necessary to identify bacterial co-infections.	Breiteneder[45] et al, 2020
Empirical Antibiotic Therapy	In severe COVID-19 cases with clinical suspicion of bacterial co-infections, healthcare providers may initiate empirical antibiotic therapy while awaiting diagnostic test results. However, this should be done with caution, and antibiotics should be tailored once culture results become available.	Sharifipour[46] et al., 2020
Antibiotic Stewardship	Antibiotic stewardship programs are essential to ensure the appropriate use of antibiotics. These programs aim to optimize antibiotic prescribing, reduce unnecessary antibiotic use, and minimize the development of antibiotic resistance.	Dyar[47] et al., 2017
Duration of Antibiotic Therapy	The duration of antibiotic therapy should be based on the specific bacterial infection and clinical response. Antibiotics should not be prescribed for longer than necessary to minimize the risk of antibiotic resistance.	Lucien[48] et al., 2021

On the other hand, *aspergillosis* is increasingly detected in healthy people suffering from severe respiratory infections caused by viruses such as influenza. *Aspergillosis* of the lung associated with COVID -19 has been described in several recent studies.[16]

COVID -19-Associated *mucormycosis* is a serious public health problem in India but is sometimes incorrectly referred to as "black fungus".[49] *Mucormycosis* is an opportunistic fungal infection caused by molds of the order Mucorales, primarily *Rhizopus* species. It usually affects individuals with weakened immune systems, uncontrolled diabetes, or pre-existing health conditions.[25] COVID -19 can weaken the immune system and makes people more susceptible to opportunistic infections such as *mucormycosis*. Cases of *mucormycosis* associated with COVID -19 have also been reported from countries other than India (including the United States), but rarely. Both poorly controlled diabetes and excessive steroid use in the treatment of COVID -19 contribute significantly to the risk. Patients with mucormycosis often test negative for invasive *aspergillosis* biomarkers such as beta-d-glucan and galactomannan. Surgery and antifungal medications such as amphotericin B, posaconazole, or isavuconazole are often used together to treat *Mucormycosis* (Table 1B). Treatment of *mucormycosis* with voriconazole is not recommended. COVID -19 *mucormycosis* may benefit from therapeutic drug monitoring.[25,50]

3.1. Viral Co-infection

In the wake of the COVID -19 pandemic, which was primarily caused by the SARS-CoV-2 virus, concerns have arisen about the possibility of coinfection with other respiratory viruses. Coinfection with SARS-CoV-2 and other viruses can significantly alter the severity of illness, the accuracy of diagnosis, and the effectiveness of public health interventions.[31] Symptom severity may be increased when SARS-CoV-2 is co-infected with another respiratory virus. For example, pneumonia and respiratory failure become more likely when co-infected with influenza and Respiratory Syncytial Virus (RSV). It can be difficult to distinguish COVID -19 from other respiratory viral infections by looking only at the following the patient's symptoms.[34,51] COVID-19 shares symptoms with several other respiratory viruses, such as fever, cough, and sore throat.[32] This makes diagnosis more difficult and requires thorough testing for multiple viruses. Multiple respiratory viruses in circulation at the same time increase the risk of overlapping pandemics, particularly in the colder months.[19,52] The burden on healthcare systems from dealing with co-infections increases during these times (Table 1C).

4. Superinfections

Superinfections, also known as secondary infections, are a significant problem for patient care and public health response.[38] Superinfections are infections that occur concurrently with a continuing primary infection, such as COVID -19. Superinfections, which can be caused by bacteria or fungi, can further exacerbate the clinical course of COVID -19, leading to worsening symptoms and prolonged hospitalizations. The first behavioural implication is the critical need for prudent use of antibiotics and antifungals to effectively treat these superinfections and prevent the emergence of antibiotic resistance.[39] Second, effective infection control methods in healthcare facilities and other initiatives to prevent superinfections are paramount.[53] Maintaining antibiotic efficacy while improving patient outcomes is a delicate balancing act that must be accomplished given the multiple threats posed by COVID -19.[40]

5. Antibiotic Resistance

The co-occurrence of multiple co-infections with COVID-19 raises a concerning spectre: antibiotic resistance. As COVID-19 patients with severe symptoms often receive empirical antibiotic therapy to guard against bacterial co-infections, the widespread use of antibiotics becomes inevitable. This overuse, combined with the complexity of managing multiple co-infections, can fuel the development of antibiotic-resistant bacterial strains. Antibiotic resistance is a global health crisis, compromising our ability to treat common infections effectively. Consequently, the careful selection and monitoring of antibiotics, along with advanced diagnostic methods to differentiate viral from bacterial infections, become paramount. Striking a balance between treating co-infections appropriately and curbing antibiotic resistance is a delicate challenge that healthcare systems worldwide must navigate during the COVID-19 pandemic.[38,45]

Although the discovery of antibiotics has undoubtedly saved countless lives, the alarming rate at which resistant strains of disease-causing bacteria are proliferating is of great concern. The decline in new drug research by the pharmaceutical sector as a result of reduced economic incentives and stricter regulatory requirements has contributed to the antibiotic resistance crisis. Antibiotic-resistant diseases have spread far beyond the United States. It is becoming increasingly clear that ARGs are not the only cause for concern in clinical infections.[54] The resistome is a reservoir for Horizontal gene transfer (HGT) through which pathogenic bacteria can acquire resistance, including ARGs in pathogenic commensal, ambient, mobile genetic elements, and bacteriophages. Recent studies have highlighted the growing public health threat posed by the increasing ability of bacteria to develop defenses against

antimicrobial agents.[47,55]

Empiric antibiotic therapy, i.e., administration of antibiotics without a confirmed diagnosis to COVID -19 patients with suspected bacterial coinfections, has become a common strategy for treating these complex cases. However, this approach raises concerns. While it is critical to treat potential bacterial coinfections promptly, empiric use of antibiotics may contribute to antibiotic overuse and the development of antibiotic resistance.[46] COVID -19 Patients often receive a range of treatments, including antiviral medications and corticosteroids, making antibiotic choice difficult because of potential drug interactions. To optimize patient care and curb antibiotic resistance, healthcare providers must choose antibiotics wisely based on clinical judgment, local epidemiology, and available diagnostic information. The goal is to strike a balance between treating coinfections quickly and maintaining the effectiveness of antibiotics in the fight against bacterial diseases.[48]

6. Conclusion and Future prospects of multiple co-infections with COVID-19

The complex and ever-changing nature of healthcare is reflected in future opportunities for COVID -19 the management of numerous co-infections. Rapid and accurate diagnostic methods that can distinguish between viral and bacterial or fungal coinfections are urgently needed. Accurate treatment decisions can benefit from recent developments in point-of-care diagnostics and biomarker identification. With regard to treatment, it will be critical to strengthen antibiotic and antifungal stewardship programmes. To curb the spread of antibiotic-resistant bacteria, health systems must priorities the rational use of these treatments, individualizing treatment plans for each patient, and eliminating wasteful overuse. Co-infections during the pandemic COVID -19 can be minimized by widespread vaccination against common respiratory illnesses such as influenza, which can help reduce the need for hospital resources. In addition, the numerous studies to be conducted during COVID -19 on the epidemiology, clinical course, and outcomes of coinfection will provide useful information for improved patient care. It is critical to learn how different infections interact in the human body. Lessons learned from the pandemic COVID -19 will be useful for future prevention efforts. To better address coinfections during a pandemic, health care systems and public health organizations will collaborate to develop protocols, recommendations, and resources. Health care providers will benefit from having access to up-to-date treatment guidelines for COVID -19 coinfections, as this will allow them to make more informed decisions and reduce the likelihood of adverse outcomes. There will be an increasing need to optimise outcomes by tailoring treatments to individual patients, taking into account their unique medical history and susceptibility to coinfection. Managing numerous COVID -19 coinfections is a complicated task that requires continued study, collaboration among health professionals and researchers, and adaptation of treatment options based on new data. As knowledge of these coinfections increases, health systems will be better able to provide efficient care to patients in a changing health care landscape.

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8. Conflict of Interest

None.

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