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Review Article

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SARS Cov-2 and Microbial Coinfection (with an Emphasis on Bacteria)

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ABSTRACT

The pandemic of the novel severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) is the main pathogenic agent of the rapidly spreading pneumonia called coronavirus disease 2019 (COVID-19) and has been posing great threats to the world in many aspects. Bacterial coinfections increase the severity of respiratory viral infections and were frequent causes of mortality in influenza pandemics but have not been well characterized in patients with coronavirus disease. This narrative, non-systematic review provides an update on the coinfection of virus and bacteria with an emphasis on bacteria- with SARS-CoV-2 and summary of their effects on COVID-19, the reasons of coinfection, and the diagnosis to emphasize the importance of microbial coinfection in COVID-19.

Keywords: SARS Cov-2, Covid-19, Coinfection, Bacterial Coinfection, Microbial Coinfection

Introduction

The coronavirus disease 2019 (COVID-19) is an infectious disease caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) that was first identified in December 2019 in Wuhan, China, and is currently circulating throughout the world. By July 5, 2020, more than 11,125,245 million cases have been diagnosed in 216 countries, and more than 528,204 deaths have been reported 0.

The severe acute respiratory syndrome coronavirus 2 (SARSCoV-2) is a novel member of enveloped RNA β-coronavirus, which is the cause of a severe pneumonia with clinical symptoms different from known coronavirus caused pneumonia, such as SARS-CoV and MERS-CoV. The SARS-CoV-2 infection has become a public health challenge for all over the world. The SARS-CoV-2 caused pneumonia was named as coronavirus disease 2019 by the World Health Organization (WHO) on 11 February 2020 0.

Since its first detection, the infection rate and mortality rate of the SARS-CoV-2 have far exceeded that of any other common flu. Many drugs and vaccines specifically targeting SARS-CoV-2 infection are under different clinical phases. The coinfection of the SARS-CoV-2 with other microorganisms, such as virus, bacteria, and fungi, is a very important factor in COVID-19, and it can raise the difficulties of diagnosis, treatment, prognosis of COVID-19, and even increase the disease symptom and mortality rate 0.

Severe acute respiratory syndrome coronavirus 2 is the cause of a devastating pandemic of COVID-19 and has led to more than 100 million cases and 2 million deaths globally in a span of 12 months. Pandemics have plagued humans throughout history but are now becoming increasingly common. Influenza was responsible for the 1918 pandemic that resulted in ~50 million deaths worldwide, and more recently pandemics in 1957, 1968, and 2009 0. In 2003, a near-pandemic of severe acute respiratory syndrome coronavirus (SARS-CoV) occurred, closely followed by the emergence of another lethal coronavirus, Middle East respiratory syndrome coronavirus (MERS-CoV), in 2012 0.

Bacterial coinfection is a common complication of many viral respiratory tract infections and leads to significantly increased morbidity and mortality. During the 1918 pandemic, bacterial coinfection was a significant contributor in nearly all influenza deaths, with common upper respiratory tract bacteria such as S. pneumoniae, β-hemolytic streptococci, H. influenzae, and S. aureus being the most common pathogens 0. Therefore, we first examine the important bacteria in coinfection with Covid-19.

Bacterial coinfection with viral respiratory infections

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Viral pneumonia and lower respiratory tract infections are well characterized in adult patients, including those diagnosed with severe forms of viral infection. Most viral lower respiratory tract infections seem to be acquired in the community and considered a leading cause of infection in patients who undergo mechanical ventilation 0. The most common cases diagnosed with bacterial co-infection with viral infections are seen in those infected with influenza virus 0.

The oldest report of bacterial infections that occurred simultaneously or shortly after influenza is related to the 1918 Influenza pandemic, in which most deaths occurred as a result of co-infection with infectious bacteria. Also, the H1N1 Influenza pandemic in 2009 was complicated by bacterial pneumonia in 4-33% of hospitalized patients 0, 0. Bacterial-viral co-infection is not restricted to influenza and also caused by other respiratory viruses, such as parainfluenza virus, respiratory syncytial virus, adenovirus, rhinovirus, and human metapneumovirus 0 0. Despite the discovery of antibiotics and viral vaccines in 1918–1957, the mortality rate, resulting from secondary bacterial pneumonia remained a major problem. The mortality rate seems to be still growing mostly because of the rapid rate of aging in the human population 0. Although viruses are commonly responsible for the development of acute upper and lower respiratory infections, in most cases patients may be infected by both bacterial and viral pathogens; however, the clinical manifestations at the early stages of the disease would not be nosologically distinguishable for physicians to differentially diagnose viral from a bacterial infection. Recently, a group of respiratory emerging viruses has been identified, such as human coronavirus (HCoV), NL63, human bocavirus, influenza viruses' type H1N1 and H5N1, SARS, Middle East Respiratory Syndrome-related coronavirus (MERS), and Covid-19 0 0.

Bacterial co-infections with respiratory viral pathogens are very common, often through synergistic interaction among viruses such as influenza virus, and bacterial pathogens and the host immune system of the human being; nevertheless, the interaction between viruses and unusual bacteria is not yet fully understood 0. These secondary infections predominantly involve a specific group of bacterial pathogens, such as S. aureus, S. pneumoniae, S. pyogenes, and H. influenzae 0. A complete list of bacterial co-infections with viral pathogens is depicted in Table 1.

Table 1

Common respiratory viral-bacterial coinfections and their associated clinical infections in human 0.

Viral infection	Bacterial coinfection	Clinical infection
Influenza	Staphylococcus aureus	MRSA Community-acquired pneumonia
	Streptococcus pneumoniae	Pneumococcal pneumonia, sepsis, meningitis
	Streptococcus pyogenes (group A)	Sepsis, pleural empyema
	Haemophilus influenzae	Pneumonia
	Moraxella catarrhalis	Pneumonia and bacteremia
	Neisseria meningitidis	Meningococcemia
	Chlamydophila pneumoniae	Pneumonia
	Mycoplasma pneumoniae	Pneumonia
	Legionella pneumophila	Pneumonia
	Klebsiella pneumoniae Pseudomonas aeruginosa	Pneumonia
	Acinetobacter baumannii Burkholderia cepacia,	Pneumonia
	Enterobacter aerogenes	Pneumonia
		Pneumonia
		Pneumonia
Metapneumovirus	Haemophilus influenzae enterococcus spp	Acute otitis media, pneumonia
	N. meningitidis group B Brucella spp	Acute otitis media, pneumonia
	Streptococcus pyogenes Streptococcus pneumoniae	Acute otitis media, pneumonia
		Acute otitis media, pneumonia
		Acute otitis media, pneumonia
		Acute otitis media, pneumonia
Respiratory syncytial virus	Pseudomonas aeruginosa	Respiratory infections in cystic fibrosis patients
Adenovirus	Haemophilus influenzae	Pneumonia or acute otitis media
	Chlamydia trachomatis	Pneumonia or acute otitis media
SARS	Chlamydophila pneumonia	Pneumonia
	Mycoplasma pneumonia	Pneumonia
MERS	Mycobacterium tuberculosis	Immune suppression and augment the infection of each othe

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Although numerous studies performed on viral and bacterial co-infections, little information exists about human coronaviruses. In addition to seasonal influenza, it has been reported corona pathogens of pneumonia include coronavirus 229E, NL63, OC43, SARS, MERS, and SARSCoV-2. These viruses can cause coinfection in the setting of community-acquired bacterial pneumonia 0 0.

Human coronavirus NL63 (HCoV-NL63) has been recently discovered as a human respiratory pathogen with a high worldwide prevalence 0. Arguably, HCoV-NL63 is among the most clinically significant human coronaviruses and associated with upper and lower respiratory tract infections, frequently occurring in the winter and presenting more severe symptoms in children, the elderly, and immunocompromised patients. In a study conducted by Golda et al.0 they evaluated the impact of HCoV-NL63 on bacterial adherence causing respiratory tract diseases. HCoV-NL63 infection has been shown to enhance the adherence of S. pneumoniae to cells infected with the virus 0. In one study, Zahariadis et al.0 showed the coinfection of SARS patients with other pulmonary pathogens. They found that 30 and 9% of cases with SARS were co-infected with C. pneumoniae or M. pneumonia, respectively. Additionally, Alfaraj et al. 0 reported the coinfection of MERSCoV with tuberculosis (TB) in two cases. In a study carried out by Wang et al.0 they reported seven cases of SARS-related deaths who developed a secondary bacterial infection 0. The COVID-19 pandemic caused a large number of immunocompromised individuals to be hospitalized and some reports indicated that some COVID-19 patients were diagnosed with secondary infections. The specific source and nature of these infections have not yet been fully investigated; however, there is evidence indicating that multidrug-resistant bacteria are among those microbes responsible for the development of these secondary infections 0. The management of the severe form of SARS-CoV-2 is similar to most viral pneumonia-causing respiratory failure. In a study carried out by Bordi et al.0 they detected M. pneumoniae in five patients (4.0%), while only one patient was infected with L. pneumophila and S. pneumoniae (0.8%), and mixed infections were also observed in a small number of cases. They found the importance of using a broad spectrum molecular diagnostic panel for rapid detection of the most common respiratory pathogens to improve evaluation and clinical management of patients with a respiratory syndrome consistent with COVID-19 0. A list of bacterial coinfection with COVID-19 is depicted in Table 2.

Table 2

List of bacterial co-infection with COVID-190.

Bacterium	Infection
Staphylococcus aureus	Necrotizing pneumonia
Mycoplasma pneumoniae	Exacerbate clinical symptoms, increase morbidity and prolonged intensive care unit stay.
Legionella pneumophila	Pneumonia
Enterobacter cloacae	Pneumonia
Acinetobacter baumannii	Pneumonia
Klebsiella pneumoniae	Pneumonia
Mycoplasma pneumoniae	Interstitial pneumonia
Streptococcus pneumoniae	Not reported
Prevotella	Not reported
Haemophilus	Not reported
Lautropia	Not reported
Cutibacterium	Not reported

Coinfection with bacteria has a great influence on the progression and prognosis of the disease, especially in severe patients, which can lead to increased needs for intensive care, antibiotic treatment, and increased deaths 0. In 2007, in the study of Bordetella pertussis and SARS-CoV coinfection, the gross and histopathological lung lesions of the coinfected group were more serious, and the coinfected group significantly upregulated the expressions and periods for proinflammatory cytokines, especially IL-6 and MCP-1 0 indicating that there is a synergistic effect between B. pertussis and SARS-CoV, which may partially explain the increased severity of pneumonia in patients with B. pertussis and SARS-CoVcoinfection. Coinfection can increase the degree of systemic inflammation in the patient, thereby increasing the severity of the disease and delaying the cure time. In patients with COVID-19, the number of proinflammatory cytokines associated with severe lung injury, especially IL-6, has increased significantly 0. Moreover, the bacterial coinfection was associated with a 2.5-fold increase in the risk of death in SARS-CoV-2 0 indicating that there is a certain interaction between bacteria or fungi and SARS-CoV-2 0.

Viral coinfection with SARS Cov-2

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Among viral infections of respiratory diseases, coinfection with other viruses is common. Many clinical studies have observed the viral co-infection with SARS-CoV-2 from different countries 0. conducted in vitro tests on 186 patient samples randomly selected from January 20 to February 1 in Shenzhen Third People's Hospital. Of the 92 SARS-CoV-2 positive patients, 6 patients (3.2%) respectively detected viral coinfection. Four of them (2.2%) detected at least two viruses 0. The common respiratory viruses including RSV, hRV, hMPV, parainfluenza virus type 2 (PIV2), and coronavirus HKU1 (HKU1) were also simultaneously detected. This data is consistent with a study of 5700 subjects that entero/rhinovirus and non-SARS-CoV-2 Coronavirus are the most common coinfected viruses, followed by RSV, parainfluenza 3, chlamydia pneumoniae, hMPV, influenza A, and mycoplasma pneumoniae 0.

Another study in Wuhan showed that among 2745 SARS-CoV-2-positive patients, 5.8% of patients had coinfections with other coronavirus, influenza A virus, hRV, and influenza A H3N2 0. In Northern California, the researcher counted that in 116 specimens positive for SARS-CoV-2, 24 (20.7%) were positive for one or more additional pathogens, and entero/rhinovirus, RSV, and nonSARS-CoV-2 Coronaviridae are the most common coinfected pathogens 0. Coinfection with other respiratory viruses may be an important reason for COVID-19's early misdiagnosis as influenza for they almost have the same clinical manifestations, laboratory, and imaging findings 0. Due to the strong infectivity and wide spread of SARSCoV-2, in addition to other respiratory viruses coinfect with SARS-CoV-2, many systemic infectious virus, such as HIV 0 and hepatitis virus 0 coinfection, are also reported and raised the serious concern, but the infection rates are still unclear. Among the viral coinfected population, the number of middle-aged and elderly people is relatively large, which may be related to their immunity and systemic disease status 0. Wang et al. 0 found that the majority of COVID-19 patients were around 30–60 years old; the overall median age was 47, while the median age of patients with coinfection was 51. However, it is worth to notice that patients with SARS-CoV-2 coinfected with other viruses are not just elders or people with systemic diseases, healthy children, youth, and middle-aged people are also at risk from the coinfection 0. A list of Viruses coinfection with COVID-19 is depicted in Table 3.

Table 3

List of Viral co-infection with COVID-19 0.

Viruses	Infection
Chlamydia pneumoniae	Pneumonia
Coronavirus (nonCOVID-19)	Pneumonia
Coronavirus HKU1 (HKU1)	Pneumonia
Entero/rhinovirus (hRV)	Pneumonia and Diarrhea
H1N1, H3N2, Influenza A	Pneumonia, headache and other
Human metapneumovirus (hMPV)	Pneumonia
Metapneumovirus	Pneumonia
Mycoplasma pneumoniae	Pneumonia
Parainfluenza 1/2/3/4	Pneumonia
Respiratory syncytial virus (RSV)	Pneumonia

The probability of respiratory virus coinfection varies from 10 to 68% 0. Coinfection increases the levels of C-reactive protein (CRP) and procalcitonin (PCT) 0. The coinfection mechanisms include virusinduced airway damage, reduced mucociliary clearance, and damage to the immune system. Since many viruses can destroy the airway epithelium, this may cause an increase in viral coinfection. Viruses can also cause immune system disorders topromote the possibility of infection by other viruses 0. At present, it is difficult to determine the kinetics of viral coinfections since there is very little information about the virus kinetic parameters of SARS-CoV-2 infection. Current reports show that the coinfection rate of SARSTable CoV-2 with other viruses is not high. The reason for this may be that the competitive advantage plays an important role in the coinfection process of SARS-CoV-2 and other respiratory viruses 0. In order to avoid the coinfection of SARS-CoV-2 and other viruses, the most important step is the prevention and control of infection. To prevent the spread of infection, social distancing should be encouraged. In the process of diagnosis and treatment for patients with other viral coinfections, it is best to provide a separate room for special people in the clinical setting to isolate and treat after understanding the risk of infection transmission. Particularly, the patients, who previously infected with an HIV virus, are more likely to cause SARS-CoV-2 coinfection when the systemic immunity declines and specific antibody responses were delayed or even vanished. Therefore, for these patients, the

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importance of isolation should be more emphasized 0.

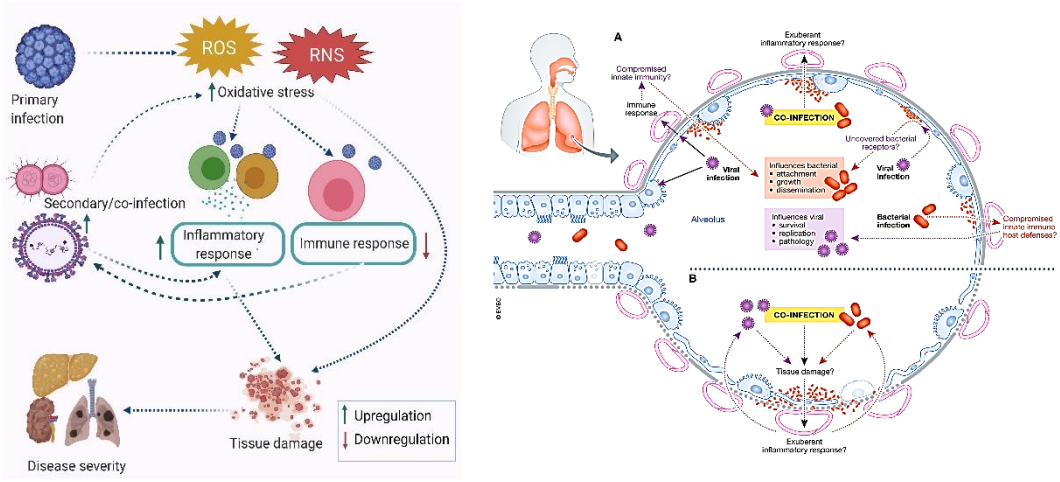
Diagnosis and Treatment of SARS Cov-2 Coinfections

Bacterial coinfections

For the diagnosis of COVID-19 patients, there are a lot of clinical guidelines. However, little attention was paid to the bacterial and fungal coinfection of this disease, and the standardized testing process of coinfection is still unavailable. It is difficult to distinguish bacterial or fungal infections from existing viral pneumonia based on clinical and radiological performance 0. In addition, there are articles indicating that calcitonin may also be an auxiliary means for detecting whether there is bacterial coinfection as the concentration of interleukin (IL)-1β, tumor necrosis factor (TNF)-α, and IL-6 increases, which results in the massive production and release of parathyroidderived calcitonin during bacterial infection. However, the synthesis of parathyroid-derived calcitonin is inhibited by (TNF) -γ, which secretion is increased during viral infection 0. Therefore, the large increase of calcitonin will reflect the overlapping infection of bacteria in patients who have developed serious diseases, leading to the complication of clinical conditions 0. In addition, the microbiological examination is a practical way for diagnosis, especially sputum culture 0. However, taking sputum or blood samples from SARS-CoV-2 infected patients may pose a significant risk to biological sample collectors and laboratory technicians as the SARS-CoV-2 does not only spread through respiratory droplets and direct contact but also through virus-laden aerosols 0. Therefore, it is very necessary to establish a standard detection measure for the coinfection of bacteria and to provide adequate protective measures for relevant persons.

Viral coinfections

Among the SARS-CoV-2 patients, fever is the most common symptom, and more than 90% of patients have a fever (Singhal, 2020); more than half have a cough (69.8%), followed by dyspnea (34.5%), myalgia (27.7%), pharyngalgia (17.4%), headache (7.2%), diarrhea (6.1%), sore throat (6.1%), and rhinorrhea (4.0%) 0. The radiological imaging features of COVID-19 pneumonia include lung changes, for example, the ground-glass opacity (GGO) changes, and bronchial changes and pleural changes. In addition, laboratory data indicated that SARS-CoV-2 infection included lymphopenia, prolonged prothrombin time (PT), the elevation of lactate dehydrogenase (LDH), alanine aminotransferase (ALT), aspartate aminotransferase (AST), D-dimer, neutrophils, eosinopenia, C-reactive protein (CRP), and troponin 0. The most common laboratory findings are a decreased lymphocyte count and an increased high-sensitivity C-reactive protein level 0. When combined with other viral infections, these results may change. The report shows that when SARS-CoV-2 and influenza A virus were coinfected, lymphocytes were increased, and C-reactive protein was often detected while the trend of lymphocytes was the opposite of SARS-CoV-2 infection alone. Of course, the results of laboratory tests are often affected by the degree of disease progression and the pathogens infected by the patient, so they can only be used as a reference for disease diagnosis 0. However, this method may cause some false negative results due to some factors during sample recovery, processing or transportation. Therefore the clinician has to repeat nasopharyngeal testing in order to confirm the diagnosis 0. For patients with high clinical suspicion, sputum samples, or bronchoalveolar lavage should be considered in diagnosis 0. However, many questions remain about how bacteria and viruses interact to cause coinfection (Figure 1).



I. II.

Figure 1. I. Co-infection modulating oxidative stress, immune response, and disease severity 0. **II.** The relationship between SARS-CoV-2 in coinfections, bacteria, and the host

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Conclusion

Respiratory viruses such as SARS-CoV-2 are wellcharacterized to cause severe disorders and pneumonia, particularly in individuals with serious medical comorbidities and aged populations. Additionally, respiratory virus infection could usually lead to enhanced susceptibility to secondary bacterial infections. The coinfection between different microorganisms and SARS-COV-2 is a serious problem in the COVID-19 pandemic. However, there are few reports about SARS-CoV-2 coinfects with bacteria, fungus, and other viruses. The clinical data of SARS-CoV-2 coinfection are of great value in guiding evidence-based treatment of COVID-19.

Additionally, recently it has been found the microbiome diversity shapes our immune system. In line with this, the depletion of the gut microbiome hinders the immune system's ability to create a humoral response against viruses like the flu virus. However, this novel paradigm ultimately allows the development of new immune intervention approaches for the prevention and management of viral-bacterial co-infections in COVID-19 patients. The COVID-19 pandemic reinforces the importance of preventative measures such as vaccination and antimicrobial treatments in maintaining human health.

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