REVIEW

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# Microbial co-infection of COVID-19 and therapeutic implications: literature review

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## ABSTRACT

**Background:** Attention to Covid-19 is shedding the role of co-infected microbial, bacteria, fungi, and non Covid-19 viruses. The presence and role of co-infected microbial is not fully understood. This review aims to find information about Covid-19 co-infected microbial, and to relate the findings with therapeutic implementation of Covid-19.
**Method:** Relevant articles were searched from PubMed and then screened. Fifty articles were reviewed to answer the objectives.
**Result:** Covid-19 infection involves co-infection of bacteria, yeast, fungi and viruses. The composition of the co-infected microbiome depends on the phase of the covid-19 infection, comorbid diseases, such as diabetes, and aging. This co-infection is associated with the phase and level of severity of Covid-19 infection.
**Conclusion:** Analysis of possibility of co-infection is strongly needed in all phases of Covid-19 and has therapeutic implications for Covid-19.

**Keywords:** co-infection, COVID-19, microbiome, Pneumonia, SARS-CoV-2.
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## INTRODUCTION

Coronavirus disease 2019 (COVID-19) is an infectious disease caused by Severe Acute Corona Virus 2 (SARS-CoV-2). This disease is classified as a new disease that has emerged where the new β-corona virus variant is still spreading worldwide.[1] Coronavirus disease 2019 has a higher infection rate than the common cold and a higher death rate.[2] The risk of death is also exacerbated in COVID-19 patients with a history of other comorbid diseases such as heart, lung, or other infectious diseases.[3]

Several studies have shown the identification of other microbes in samples to diagnose COVID-19 in several laboratory tests. The presence of co-infection with SARS-COV-2 and other pathogens has been studied in previous studies.[4] The issue of co-infection is a major concern in COVID-19 because co-infection with other microorganisms, such as bacteria, fungi and viruses, can intensify the problems of diagnosis, treatment and prognosis of COVID-19. However, another study has shown contrasting results, where there has been an improvement in symptoms and risk of death from COVID-19 with co-infection.[5] Currently, many traces and investigations show a strong relationship between viruses, bacteria, fungi, and other coronaviruses and SARS-CoV2.[6]

Several previous studies have reported that co-infected and comorbid COVID-19 are associated with poor outcomes in COVID-19 patients. Data on co-detected microbial pathogens in COVID-19 patients are not always available, but co-infection with microbial pathogens has been found in clinical settings.[7] In addition, information about targeted therapy for SARS-CoV-2 infection is not fully understood in the various clinical phase conditions. Therefore, this review aimed to gather information on the microbiome of COVID-19 co-infection and relate these findings to therapeutic applications in COVID-19.

## METHOD

We conducted an observational and analytical study by systematically searching four databases: NEJM, Medscape, Medline, and PubMed. Articles were selected according to the eligibility criteria using the keywords COVID-19 and co-infection until 31 August 2020. It is hoped that the article can summarize the co-infection relationship, implications, and how to diagnose pathogens and SARS-CoV-2 in COVID-19. We obtained 329 articles from the database, then obtained 10 relevant articles after a screening and analysis process that could answer the objectives.

## RESULT

We resumed from all the articles included in the study, where we got nine groups of pathogens detected by Real Time-PCR (Table 1). In addition, three companies provide PCR multiplex panels (Table 2). The management of COVID-19 can be adjusted according to the infection phase, which consists of early, first, second, second and third, and all stages, which at each stage have different kinds of drugs (Table 3).

## DISCUSSION

### Microbial Coinfection of Covid-19 Infection

Co-infection is a condition where other infections simultaneously overlap other than the basic infection. Respiratory

symptoms occur in around 20% of hospitalized patients, of which the majority (58.5%) are positive for SARS-CoV-2, and the rest (42.5%) are infected with other common respiratory viruses. In such cases, co-infected patients show mild symptoms.[13] On the other hand, pediatric patients are more frequently reported with co-infection.[14]

Bacteria, fungi and other viruses are the pathogens that dominate the majority of co-infections in SARS-CoV-2.[15] The prevalence of co-infected COVID-19 patients can vary, where the prevalence of secondary co-infection was found to be 50% in patients who did not survive. Procalcitonin levels greater than 0.5 ng/ml have been reported in three of four patients with secondary co-infection, where these levels suggest a bacterial infection. The co-infection marker with only procalcitonin levels as a marker of bacterial infection in COVID-19 requires further validation.[16] COVID-19 patients with critical conditions such as moderate to severe ARDS have been associated with invasive pulmonary aspergillosis due to Aspergillus fungal infection.[17,18]

Studies show that bacterial co-infection is found in 7% of 3,834 hospitalized COVID-19 patients, whereas ICU patients have a high prevalence of 14%. *Staphylococcus aureus*, *Streptococcus pneumoniae*, and *Streptococcus pyogenes*, bacteria that colonize the nasopharynx, have been reported to be associated with influenza infection. The first 6 days of influenza is the most common onset of secondary co-infection.[19] In contrast, another study showed that *Pseudomonas aeruginosa*, *Mycoplasma pneumoniae*, and *Haemophilus influenza* were the most

**Table 1. The respiratory pathogen that can be detected with Real Time-PCR.[8]**

| No | Group | Virus' Name |
|---|---|---|
| 1 | Influenza | Influenza A (FluA), Influenza B (FluB) |
| 2 | Parainfluenza virus | Parainfluenza type 1, 2, 3 and 4 (PIV1, 2, 3, 4) |
| 3 | Respiratory Syncytial Virus (RSV) | Respiratory Syncytial Virus (RSV) |
| 4 | Metapneumovirus Manusia (HMPV) | Metapneumovirus Manusia (HMPV) |
| 5 | Coronavirus | Coronavirus 229E, NL63, OC43 and HKU1 (HCoV – OC43, HCoV-229E, HCoV-HKU1, HCoV-NL63), SARS-COV, MERS-COV |
| 6 | Adenovirus | Human Adenovirus (HAdV), Human Bocavirus Adenovirus (HBoV) |
| 7 | Rhinovirus | Human Rhinovirus (HRV) |
| 8 | Cytomegalovirus (CMV) | Cytomegalovirus (CMV) |
| 9 | Herpes Simplex Virus (HSV) | Herpes Simplex Virus (HSV) |
| 10 | Epstein Bar Virus (EBV) | Epstein Bar Virus (EBV) |
| 11 | Bacteria | *Chlamydia pneumoniae* (CP), *Legionella pneumoniae* (LP), *Mycoplasma pneumonia* (MP), *Haemophilus influenzae* (Hi), *Klebsiella pneumoniae* (KP), *Moraxella catarrhalis* (MC), *Streptococcus pneumoniae* (*S. pneumoniae*), *Escherichia coli* (*E. coli*), *Mycobacterium tuberculosis* (TB), *Staphylococcus aureus* (*S. aureus*), *Pseudomonas aeruginosa* (*P. aeruginosa*), *Acinetobacter baumannii* (*A. baumannii*), *Bordetella pertussis, Pneumocystis carinii* (PC) |
| 12 | Fungi | *Aspergillus*, *Cryptococcus neoformans* A and B, *Cryptococcus*, *Histoplasma capsulatum*, *Candida*, and *Mucor* |

**Table 2. PCR multiplex panels to assist in the early diagnosis of possible respiratory pathogens.**

| No | Kit Name | Company |
|---|---|---|
| 1 | Luminex NxTAG respiratory pathogen panel | Luminex Corporation |
| 2 | Luminex xTAG RVP Fast | |
| 3 | Luminex xTAG RVP v1 | |
| 4 | Verigene Respiratory Pathogens Flex test | |
| 5 | RVP eSensor | GenMark Diagnostics |
| 6 | ePlex respiratory pathogen panel | |
| 7 | Film Array breathing panel | BioFire Diagnostics |

**Table 3. Treatment for each stage of COVID-19 infection.[9–12]**

| No | Stage | Treatment | Function |
|---|---|---|---|
| 1 | Early | Convalescent plasma (antibodies containing antibodies from recovered COVID-19 patients) | Reduce the number of virus particles in the body in the early phase of infection |
| 2 | First | Remdesivir (GS-5734), a nucleoside analogue, has been shown to inhibit highly pathogenic animals and humans' coronaviruses, such as MERS-CoV and SARS-CoV. This antiviral has also been shown to inhibit COVID-19 in vitro. | Interrupt viral replication |
| 3 | Second | Tissue plasminogen activator (tPA) — a drug used to treat stroke | Breaks up blood clots in phase 2 |
| 4 | Second and third | Inflammation-fighting medications (tocilizumab, corticosteroids and sarilumab) | Reduce system-wide inflammation |
| 5 | All stage | Anti-clotting drug heparin | Prevent blood clots in blood vessels and capillaries. |

common bacteria causing co-infection, while 3% were caused by co-infection viruses such as Respiratory Syncytial Virus and influenza A.[20]

Overall, the proportion of bacterial co-infection in COVID-19 patients was lower than in previous influenza pandemics, where bacteria such as *S. pneumoniae*, *S. aureus* or *S. pyogenes* played the main role in co-infection. These findings support the discontinuation of empirical antibiotics in the majority of patients diagnosed with COVID-19.[11] Examination with real-time RT-PCR was carried out to detect SARS-CoV-2;[8] also, real-time pathogen-specific RT-PCR can be used to detect thirty-nine other respiratory pathogens (Table 1).[21]

PCR multiplex panels were approved by the US Food and Drug Administration (FDA) for early detection of suspected respiratory pathogens before the emergence of the COVID-19 pandemic (Table 2).[22] The possibility of co-infection with SARS-COV-2 cannot be ruled out when using the test panel to detect respiratory pathogens. In the end, only one respiratory pathogen was detected since the reports of different PCR results for SARS-COV-2, where the initial results were reported negative and then positive on re-examination.[23] The good news is that preexisting multiplex syndrome panels such as Bio Fire Film Array RP-2.1 (Bio Fire Film Array Respiratory Panel-2 plus SARS-CoV-2; bioMerieux, France) and QIAstat-Dx Respiratory Panel® 2019-nCoV (Qiagen, Netherlands) were able to enter a sample of SARS-CoV-2 quickly. Using the QIAstat-Dx® Respiratory Panel 2019-nCoV can simultaneously identify many other common respiratory pathogens, such as bacteria and viruses, except for SARS-COV-2. Thus, co-infection cases can be reduced which were previously undetected during the COVID-19 pandemic (Table 2).[24]

## Clinical Symptoms of COVID-19

The microenvironment of the respiratory organs is significantly affected by the COVID-19 infection. In general, based on guidelines related to the diagnosis and treatment of new coronavirus pneumonia issued by the Chinese National Health Commission, it is reported that the initial symptoms that arise may include headache, cough, fever, and fatigue.[16,25] The incubation time was an average of 6.7 days. The time from the onset of symptoms to visiting the hospital and from the visit to being confirmed was 4.5 and 2.1 days, respectively.[25] The infection can heal by itself, so patients with mild signs and symptoms generally do not need additional examinations or may not need to undergo a COVID-19 test, but this again depends on their risk profile. COVID-19 patients with comorbid co-morbidities who have mild symptoms may experience a rapid worsening of clinical symptoms approximately one week after the onset.[25]

## Implication Co-Infected Microbiome on The Covid-19 Therapy

### Drugs for Covid-19 treatment

There are three different phases, with each having varying symptoms of COVID-19. Pathophysiological interactions with the virus play an important role in the characteristics of each phase. The treatment plan that will be made and given to the patient should be adjusted to the stage of the infection that is occurring so that the administration of drug administration and potential treatment to the patient can be personalized. Based on Venu Madhav Konala's argument stated that COVID-19 is different from influenza. Treatment of COVID-19 cannot use drugs for influenzas such as Oseltamivir, Zanamivir, Peramivir and Baloxavir.[26] Currently, safety and effectiveness tests for drugs for COVID-19 have been carried out and developed, so further research support is needed, especially concerning specific treatments for each phase of the disease.

Previous studies have reported using several treatments for each stage of infection, such as convalescent plasma (antibodies from recovered COVDI-19 patients), Remdesivir, tissue plasminogen activator (tPA), anti-clotting drugs heparin, and anti-inflammatory drugs such as tocilizumab, corticosteroids. and sarilumab (Table 3). However, antivirals such as Remdesivir and other antivirals still require further investigation regarding the safety of use in adult severe COVID-19 patients.[9,10,12] Cytokines are known to have an important role in the pathogenesis of immune-associated pneumonitis, so cytokine-related therapeutic targets such as interleukin 6 (IL-6) and tumor necrosis factor-α are promising targets. They can be developed as specific antiviral treatments which currently do not exist.[11] In addition, several types of COVID-19 vaccines have also been given to everyone to control the pandemic.

### Drugs for the co-infection of non-COVID-19 viruses and microbiota

Patients infected with COVID-19 can get worse with co-infection. Co-infection can significantly reduce the function of the adult immune system, thereby increasing tolerance to antibacterial therapy and worsening the disease prognosis.[12] About 94.2% of COVID-19 patients may be co-infected with one or more pathogens.[27] Research shows no difference in co-infection rates between women and men, meaning men and women are equally susceptible to other respiratory pathogens. In addition, the incidence of co-infection was found to be increased in patients aged 15-64 years compared to patients aged <15 years and >65 years. This is because in this age range, it was found to have higher rates of influenza co-infection, HadV, and HRV. In contrast, previous studies stated that the pathogen primarily affects young people and the elderly.[27] This difference is related to the decrease in immunity that occurs after.

The risk of co-infection can be reduced by proper treatment of COVID-19 patients. This can be seen from co-infection within 1-4 days of onset after being positive for COVID-19. A high co-infection rate occurs on day 4, so asymptomatic COVID-19 patients can also be co-infected.[3] Treatment must be adjusted according to pathogen findings, such as in the case of COVID-19 with pulmonary aspergillosis (CAPA). Pulmonary aspergillosis can increase the risk of ARDS in COVID-19 patients.[10,28] In addition, establishing the diagnosis of CAPA is challenging because sampling via bronchoscopy increases the risk of transmission of COVID-19, which results in difficulties in selecting drugs and complicates CAPA treatment. The drug therapy given to patients can interact with each other;[17] therefore, this clinical reality condition triggers the urgency of developing new antifungal drugs

through promising pharmacokinetics and pharmacodynamics. In non-COVID-19, the most common infection is influenza virus infection, and treatment has been carried out with influenza antivirals. However, there is not much information related to antibiotics that eradicate aspergillus, candida/yeast, and both gram-positive and negative bacteria.[28]

## CONCLUSION

Co-infection between microorganisms and SARS-COV-2 is a serious problem in the COVID-19 pandemic. However, reports of SARS-CoV-2 co-infection with bacteria, fungi, and other viruses are invaluable in guiding evidence-based COVID-19 treatment. Patients with severe SARS-CoV-2 infections have much higher co-infection rates than those who are not seriously affected. Medical personnel must identify the infections exposed to patients to provide good treatment and avoid resistance.

## DISCLOSURES

### Funding
Not available.

### Conflict of Interest
There is no conflict of interest.

### Author Contribution
WDG and KH involved in concepting, designing, and supervising the manuscript. KH conduct the study. WDG analyses the data. All authors prepare the manuscript and agree for this final version of manuscript to be submitted to this journal.

### Ethical Approval
Not available.

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