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NARRATIVE REVIEW – OPEN ACCESS

Update on COVID-19 Co-infection

Elif Şeker[1], Öner Özdemir[2]

ABSTRACT

World Health Organization data indicate that as of April 2022, 6.2 million deaths have been reported worldwide due to coronavirus disease 2019 (COVID-19). In Türkiye, official statistics indicate some 15 million cases and a death toll of 98,660. It is important that clinicians consider the possibility of the co-occurrence of other respiratory microorganisms with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, the virus that causes COVID-19, when managing treatment, particularly severe COVID-19 patients. The burden and effect of a secondary infection may be significant, especially in patients with chronic disease and advanced age. Proper attention to potential co-infections can prevent COVID-19 progression and the development of complications.

Keywords: Coronavirus, co-infection, COVID-19, pandemic, SARS-CoV-2

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[1]Department of Pediatrics, Sakarya University, Training and Research Hospital, Sakarya, Türkiye
[2]Division of Allergy and Immunology, Department of Pediatrics, Sakarya University, Training and Research Hospital, Sakarya, Türkiye

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Correspondence
Elif Şeker,
Sakarya University, Training and Research Hospital, Department of Pediatrics, Sakarya, Türkiye
Phone: +90 264 444 54 00
e-mail:
elifseker@sakarya.edu.tr

INTRODUCTION

World Health Organization official data released in April 2022 indicate that 6.2 million people worldwide have died of coronavirus disease 2019 (COVID-19), and the true number of deaths associated the pandemic is likely much greater. In Türkiye, 15 million cases have been reported, with a death toll of 98,660 (1). Early recognition of COVID-19 is important to prevent spread of the disease and initiate appropriate treatment. However, the diagnosis of COVID-19 does not exclude the presence of other respiratory pathogens, and similarly, determination of the SARS-CoV-2 pathogen does not exclude other infections. Co-infection is not uncommon and appropriate antimicrobial treatment is important.

This report is an update on our knowledge of co-infections in COVID-19, including disease frequency, microorganism types, risk factors, clinical picture, and the course of co-infections. The literature cited in this article was published within the previous 3 years and was selected primarily from the PubMed database based on a keyword search using "coronavirus," " COVID-19," "SARS-CoV-2," "pandemic," and "co-infection."

FREQUENCY and MICROORGANISM TYPES of CO-INFECTIONS ASSOCIATED with COVID-19

Many viral and bacterial co-infections have been reported in outbreaks of Middle East respiratory syndrome (MERS) and severe acute respiratory syndrome (SARS), other members of the coronavirus family. The most frequently reported microorganisms were *Chlamydophila pneumoniae*, *Mycoplasma pneumoniae*, metapneumovirus, and influenza (2–4). The most frequently reported microorganisms associated with SARS-CoV-2 are provided in Table 1.

Kim et al. (5) reported that 23 (20.0%) of 115 patients with a positive SARS-CoV-2 test were also positive for other respiratory tract pathogens. The association of SARS-CoV-2 with other respiratory pathogens has been reported to be some 30% (6). In a cohort study, it was reported that the rate was as high as 50% (7). The use of vaccines and antiviral drugs will reduce this burden (6, 8).

Lansbury et al. (9) conducted a meta-analysis of 30 studies with 3834 patients and reported bacterial co-infections in 7% of hospitalized COVID-19 patients and 14% of intensive care unit admissions with COVID-19. The most common bacteria were *Mycoplasma pneumonia*, *Pseudomonas aeruginosa*, and *Haemophilus influenzae*. The most common viruses were respiratory syncytial virus and influenza A. In 3 studies, there were reports of fungal infections.

RISK FACTORS for CO-INFECTION ASSOCIATED with COVID-19

Bacterial and fungal infections secondary to COVID-19 have been reported, and particularly in patients requiring intensive care unit care. Risk factors identified include advanced age, long-term use of antibiotics, central catheters,

Table 1. The most common microorganisms associated with SARS-CoV-2

Bacterium	Virus	Fungus
Chlamydophila pneumoniae	Metapneumovirus	*Aspergillus fumigatus*
Mycoplasma pneumoniae	Influenza A	Mucormycosis
Pseudomonas aeruginosa	Respiratory syncytial virus	*Candida albicans*
Haemophilus influenzae		*Pneumocystis jirovecii*

SARS-CoV-2: Severe acute respiratory syndrome coronavirus 2.

long hospital stay, severe sepsis, use of a mechanical ventilator, corticosteroid use, and chemotherapy (10, 11). Conditions such as diabetes, steroid-induced hyperglycemia, metabolic acidosis, a high ferritin level, the severity of COVID-19, and hypoxia can create a favorable environment for opportunistic infections, especially the development of spores and mucormycosis (12–14). The CD-4+- and CD-8+- T cell count may be low in severe COVID-19, which also creates a vulnerability to infection (12).

CLINICAL PICTURE and COURSE of CO-INFECTIONS ASSOCIATED with COVID-19

It can be difficult to distinguish COVID-19 from influenza. SARS-CoV-2 and influenza are both transmitted through respiratory droplets and the clinical presentation can be similar (fever, cough, myalgia, headache, fatigue) (8, 15, 16). Management is critical. Ground glass density, opacity, and consolidation findings on computed tomography images are associated with, but not specific to, COVID-19. These findings can also be seen in influenza and other viral types of pneumonia. Barrera-López et al. (17) reported in a literature review that the pathogen most associated with COVID-19 co-infection was influenza A. Some have observed that influenza co-infection did not affect the severity of COVID-19 (15, 16, 18–21). Notably, however, it has also been noted that the association of the influenza A virus with SARS-CoV-2 may cause false-negative results in a COVID-19 polymerase chain reaction test (7).

The impact of co-infection associated with COVID-19 is a subject of continuing study. In a study of co-infection interactions caused by respiratory pathogens, Pinky et al. (22) found that 1 virus could block the replication of another virus. For example, they observed that the very fast replicating rhinovirus reduced the replication rate of other viruses, and that the very slow replicating parainfluenza virus was suppressed in the presence of other viruses. One virus may block the growth of another virus as a result of viral interference (22). Opatowski et al. (23) found that the influenza virus inhibited the replication of other viruses, but lung tissue damage as a result of influenza increased the invasion and adhesion of bacteria. It has also been noted in other studies that the influenza virus predisposes the patient to bacterial infection (24). There are also studies reporting that viral co-infection caused more severe disease in the host. Currently, there is not yet enough data available to determine whether simultaneous viral infection in patients with SARS-CoV-2 may potentially lead to viral interference or affect the outcome of the disease (25). In general, co-infections are thought to complicate the diagnosis and treatment of severe COVID-19 patients (26).

Gervasoni et al. (27) reported that 47 patients identified as having a SARS-CoV-2 infection from a dataset of 6000 HIV-positive patients did not have a higher mortality rate than COVID-19 patients without HIV. It was considered that antiretroviral agents used in HIV therapy may have played a positive role in the course of COVID-19, however, it has been demonstrated that these drugs do not prevent SARS-CoV-2 and do not protect respiratory function (28–30). Another theory for the favorable outcomes posits that the patients retained a weak immune system following antiretroviral treatment and had some residual immune activation that reduced the development of COVID-19. However, the authors noted that these observations should be supported with larger cohort studies (27).

Zha et al. (31) evaluated groups of COVID-19 patients with and without the coexistence of *Mycoplasma pneumoniae*. The patient complaints (fever, cough, shortness of breath, fatigue, and diarrhea) were similar, but the length of cough duration was longer and risk of thrombosis were greater in the coinfected patients.

Respiratory tract viruses can damage the airways and create a vulnerability to microorganisms such as *Aspergillus* (32–34). The most commonly reported fungal infection with COVID-19 has been COVID-19-associated pulmonary aspergillosis (CAPA) (26, 35, 36). The coexistence of mucormycosis, candidiasis, and *Pneumocystis jirovecii* has also been frequently reported (35). The prevalence of mucormycosis in India, and particularly in patients with COVID-19, prompted a call to raise awareness and a suggestion that the duration and dosage of steroids be re-examined (37). Chong et al. (36) conducted a systematic review of 19 studies that included 1421 patients hospitalized due to COVID-19. They reported an overall CAPA incidence of 13.5%, with a rate ranging from 2.5% to 35%. Furthermore, coccidioidomycosis should also be considered if suspected COVID-19 is accompanied by cutaneous symptoms (38).

In a meta-analysis that included 2246 cases of COVID-19 co-infection, Soltani et al. (11) reported that 78–123 per 1000 patients had a fungal co-infection. The most common fungal microorganism was *Aspergillus*, with a prevalence of 3.71%, followed by *Candida* with a prevalence of 2.39%. The authors emphasized that it can be difficult to detect fungal co-infection in patients infected with COVID-19, which may delay appropriate treatment. They recommended routine initiation of antifungal treatment, especially for COVID-19 patients hospitalized in the intensive care unit.

The differential diagnosis of a potential COVID-19 patient should be thorough and include consideration of possible co-infections, particularly diseases that are endemic to the region. A comprehensive history and a thorough physical examination are required to detect concomitant infections. Mohamed et al. (39) reported a case of coexistence of COVID-19 and asymptomatic filariasis, which is endemic to many areas. Similarly, a case of comorbid Crimean-Congo hemorrhagic fever and COVID-19 has also been reported in Türkiye (40).

CONCLUSION

The possibility of co-infection associated with COVID-19 should not be ignored. While some may develop secondary to medical treatment or other causes, it should be kept in mind that SARS-CoV-2, a respiratory tract virus, also increases vulnerability to other infections. To prevent potentially life-threatening complications, it is important to consider, test for, and diagnose co-infections promptly and apply the appropriate treatment.

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