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Review Article

Most common concurrent infections with COVID-19

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ABSTRACT

Concurrent infections are a common complication of viral respiratory infections. They pose diagnostic challenges due to an overlap of similar symptoms, resistance to treatment and extending length of hospital stay. In this review we will extensively discuss the most common concurrent infections in patients with coronavirus disease 2019 (COVID-19). A thorough literature search was conducted in online databases such as PubMed, Google Scholar and included systematic reviews, meta-analyses, prospective and retrospective cohort studies in this review. Bacterial co-infections are the most common concurrent infections in patients with COVID-19 succeeded by viral and fungal co-infections. The prevalence of co-infections in COVID-19 patients is higher in intensive care units (ICU). Gram negative bacteria such as *Klebsiella pneumoniae*, *Pseudomonas aeruginosa* and *Escherichia coli*, whereas gram positive bacteria such as *Staphylococcus aureus* are common pathogens for bacterial co-infections. The findings for the most common viral co-infection are inconsistent however, larger number of studies report respiratory viral co-infections such as influenza and respiratory syncytial virus. Fungal co-infections in COVID-19 patients are most commonly caused by the *Candida spp*. and occur predominantly in patients admitted in the ICU and are associated with high mortality and morbidity in COVID-19 patients. Continuous research on concurrent infections occurring in COVID-19 is essential. Larger prospective studies based on stratified groups of age, gender, and both ICU and non-ICU settings should be conducted. Studies on microbial susceptibility can lend more weight to empirical antibiotic and antifungal therapy. Early diagnosis of concurrent infections in COVID-19 is imperative to prevent poor patient outcomes.

Keywords: COVID-19, Concurrent, Co-infection, Bacterial, Viral, Fungal

INTRODUCTION

Coronaviruses are single stranded positive ribonucleic acid (RNA) viruses belonging to the Coronoviridae family. In December 2019, an unfamiliar coronavirus was identified during an outbreak causing a respiratory illness in Wuhan, China.[1] It was officially named as the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) whereas the disease caused by SARS-CoV-2 was called coronavirus disease 2019 (COVID-19).[2] Due to the high

transmissibility of the virus, COVID-19 rapidly progressed as a pandemic infecting millions of people globally, leading to high in-hospital admissions, overburdening health care systems, causing more than 5 million deaths worldwide and major losses in business and productivity.[2,3]

The United States Centers for Disease Control and Prevention (CDC) describe a concurrent infection as being infected with two or more separate causative agents simultaneously causing an overlap of symptoms, therefore creating challenges in reaching a definitive diagnosis.[4,5] The term co-infection is also used throughout literature when a concurring infection occurs with the primary infection on initial presentation. Since the emergence of the COVID-19 pandemic, the role of co-infections in COVID-19 is still unclear. [6] All concurrent infections can occur in two forms. A community acquired infection (CAI), when a co-existing infection is diagnosed at the time of initial infection or within 48 hours of hospital admission, and a hospital acquired infection (HAI) occurs when a co-existing infection is not present at the time of initial infection but diagnosed 48 hours after hospital admission. HAI are also known as secondary infections or super-infections.[7] Studies have reported a 45% co-infection and rate of secondary infections in patients with COVID-19.[8]

Concurrent infections are a common occurrence in viral respiratory infections. Co-infections pose diagnostic challenges in identification due to similarities in symptoms, difficulties in management and treatment, causing an extended length of hospital stay, and even escalation of treatment to the intensive care unit (ICU) with a need for mechanical ventilation.[9] Concurrent infections often have a poor prognosis, increased morbidity and mortality especially in high-risk populations such as the immunocompromised, patients with chronic co-morbidities and elderly patients.[4] The purpose of this review is to discuss some of the most common concurrent infections occurring in patients diagnosed with COVID-19.

METHODS

An extensive research was conducted from electronic databases such as PubMed, Medline Embase, Google Scholar and Cochrane Library. To avoid missing potential studies, a further manual search for papers was done through Google Scholar. Previous studies including case reports, literature reviews, and cohort studies have been included. Only studies in English were included.

DISCUSSION

A large systematic review with 72 studies and a meta-analysis with 68 studies was conducted in Saudi Arabia. The combined studies had a total of 31,953 SARS-CoV-2 infected patients. The overall pooled proportions of SARS-CoV-2 patients with bacterial co-infections were 15.9% (95% confidence interval 13.6-18.2). The rate for viral co-infections was 6.6% whereas, fungal co-infections rates were 3.7%. In bacterial co-infected SARS-CoV-2 patients, an analysis between two subgroups of both ICU, non-ICU patients and only-ICU patients was done. The rate of bacterial co-infection was higher in the only-ICU patients' group with a rate of 22.2% (95% CI 16.1 to 28.4) whereas the rate of co-infection in both ICU and non-ICU group was 14.8%. Similarly, an analysis for fungal co-infected SARS-CoV-2 patients between the two sub-groups showed a significant difference. The rate of fungal co-infection in the only-ICU group was higher 9.6% (95% CI 6.8 to 12.4) as compared to the both ICU and non-ICU patients which was 2.7%. However, in the respiratory viral co-infected SARS-CoV-2 patients, an analysis between both subgroups showed an identical proportion between both ICU, non-ICU patients' (6.6%) and the only-ICU patients' (6.6%). Bacterial co-pathogens were reported in 49 out of 72 studies (68%), accounting for 57.3% of reported co-infections. Respiratory viral co-pathogens were reported in 44 out of 72 studies (61.1%), accounting for 39.5% of the reported co-infections, while fungal co-pathogens were reported in 16 out of 72 studies (22.2%) accounting for only 3.2% of all reported co-infections.[10]

Similar findings were observed in a systematic review and meta-analysis on co-infections in patients hospitalized with COVID-19 conducted by Lansbury et al. Out of 30 studies, 3834 patients were included. The overall pooled proportion of co-infections in hospitalized COVID-19 patients was 12%. Studies were further segregated into categories of ICU only patients and a mixed population of patients admitted both in the ward and ICU. The rate of bacterial co-infection was 7% (95% CI 3 to 12). The sub-group analysis in bacterial co-infections showed a significantly higher rate in ICU only patients with 14% (95% CI 5 to 26), as compared to a 4% in mixed hospitalized patients. A pooled analysis showed an estimated rate of 3% for viral co-infections, however, there was no statistically significant difference in the sub-group analysis in viral co-infections with a rate of 5% in the ICU only group as compared to 3% viral co-infection in the mixed patient population. Fungal co-infections with 4 pathogens were identified in only 3 studies out of 30 studies.[11] Similarly, a retrospective cohort study in Spain revealed out of 989 patients, 72 patients had 88 had co-infections, from which 74 were bacterial co-infections, 7 were viral and 7 were fungal co-infections.[12]

The difference in prevalence between bacterial and viral co-infections can also be observed in a study on co-infections among COVID-19 patients conducted in the United States. In this study, the authors Singh et al compared the rate of co-infections in SARS-CoV-2 positives to SARS-CoV-2 negatives. Out of 50,419 respiratory samples of nasopharyngeal, oropharyngeal and sputum, 4259 samples were positive with SARS-CoV-2. The rate of bacterial co-infection was 33.17% in SARS-CoV-2 positive patients, whereas the rate of viral co-infection was 3.42%. Although the rates of bacterial and

viral co-infection in SARS-CoV-2 positive patients were lower in comparison to SARS-CoV-2 negative patients (35.45 % and 8.46%), bacterial co-infection still showed predominance in comparison to viral co-infections in SARS-CoV-2 positive patients.[8] However, a few studies have reported conflicting results. Fattorini et al discuss 13 studies with 733 patients. Viral co-infections were identified in 17.2% patients (126/733) bacterial co-infections were found in 11.8% patients (86/733), whereas fungal co-infections were found in only 1.8% patients (13/733). [13] Similarly, a systematic review by Musuuza et al reported out of 118 studies, 67 had co-infections (57%). The estimated pooled prevalence rate of viral co-infections was 10% (95% CI: 6%-14%) while viral superinfections were 4%. The rate of bacterial coinfections was 8% and bacterial superinfections was 20% (95% CI: 13%-28%) whereas the rate of fungal co-infections was 4%, and fungal superinfections, 8%. A high prevalence of co-infections was observed in the non-ICU population at 29% (95% CI: 14%-46%), 18% among combined patients of ICU and non-ICU patients, whereas ICU only patients had a co-infection rate of 16%.[14]

Concurrent bacterial infections

Concurrent infections with bacterial pathogens are known to be the leading cause of mortality in pandemics such as influenza and viral pneumonias.[8,15] A retrospective-cohort observational study on the microbiological profile of hospitalized COVID-19 patients was conducted in United Arab Emirates (UAE) from February to July 2020. The results of the study reported 392 laboratory-confirmed co-infections from 29,802 COVID-19 patients. In bacterial co-infections, the most common pathogens identified were gram-negative organisms such as *Pseudomonas aeruginosa, Klebsiella pneumoniae, and Escherichia coli*, *Stenotrophomonas maltophilia*, and *Acinetobacter baumannii*. The common gram-positive organisms *were Staphylococcus epidermidis*, *Enterococcus faecalis and Staphylococcus aureus* and *methicillin resistant Staphylococcus aureus* (MRSA).[15] A similar retrospective study on bacterial coinfections among COVID-19 positive patients was conducted in Bahrain. A total of 1380 COVID-19 positive patients were included in the study of which 261 had a confirmed bacterial co-infection (19%). Gram negative bacteria was isolated from 34.7% patients, of which the most common pathogens were *Klebsiella pneumoniae*, *Pseudomonas aeruginosa*, *MDR Acinetobacter baumannii*, *Escherichia coli*, *Stenotrophomonas maltophilia* (*S. maltophilia*), and *Enterobacter cloacae* (*E. cloacae*). Gram positive bacteria were also isolated from 34.7% patients, and the most common pathogens were *Staphylococcus hominis* (*S. hominis*), *Staphylococcus epidermidis*, *Enterococcus faecium*, *Enterococcus faecalis*, and *Staphylococcus aureus.* Hospital acquired Infections accounted for 70% of which 75% were due to gram negative bacteria and 11.8% were due to gram positive bacteria.[7] According to the retrospective cohort study in Spain, 74 bacterial co-infections were identified in 61 out of 88 co-infected patients positive with COVID-19. Furthermore, in 25 patients, 30 community acquired bacterial co-infections were reported (2.5%) and were mostly due to gram positive bacteria *(S. pneumoniae, aureus, MRSA).* Similarly, 44 hospital acquired bacterial co-infections or superinfections were diagnosed in 38 patients (3.8%) and were mostly due to Gram-negative bacteria *(P. aeruginosa, E. coli*, and *K. pneumoniae).*[12] In the study by Singh et al, the infection rate of bacterial pathogens was lower in SARS-CoV-2 positive patients in comparison with SARS-CoV-2 negative patients, except, *S. aureus* which was the only bacterial pathogen that was reportedly higher in SARS-CoV-2 positives at a rate of 13.17%, as compared to SARS-CoV-2 negatives 11.64%.[8]

Concurrent viral infections

Various studies present conflicting results on common concurrent viral infections. According to the systematic review conducted in Saudi Arabia, from 61.1% studies, the most common respiratory viruses were Epstein Barr virus (EBV), human herpes virus 6 (HHV6), influenza A virus, human metapneumovirus and adenovirus. [10] Similarly, according to Singh et al, the most prevalent viral co-infection among SARS-CoV-2 positive cases was the EBV.[8] Higher EBV infections have also been reported among COVID-19 patients in Wuhan, China. EBV exists in a latent form after a primary infection and gets reactivated during periods of immunosuppression. Therefore, EBV infections can undergo reactivation during a COVID-19 infection as a result of the host's immune mediated response.[8,16] Furthermore, EBV deoxyribonucleic acid (DNA) is found in 95.2% of COVID-19 patients admitted in the medical ICU, and 83.6% of patients admitted in the surgical ICU.[16] On the contrary, according to the meta-analysis by Lansbury et al, viral co-infections were identified in 14 studies from which the most common viral co-infection was due to respiratory syncytial virus (RSV) making 16.8% of detections, followed by influenza A virus (15.5% detections).[11] Similar findings were observed in the retrospective study in Spain, where community acquired viral co-infections were detected in 7 out of 989 patients (0.6%). *Influenza A* was most common followed by *RSV* and *herpetic virus*.[12] In contrast to the above findings, according to a systematic review in Iran, out of 33 studies, 10484 patients with COVID-19 were identified. The pooled prevalence of viral coinfections was estimated to be 12.58%. The most common type of viruses among all viral co-infections were blood borne viruses (pooled prevalence: 12.48%; 95% CI: 8.57 to 16.93) whereas respiratory viruses were the least common (pooled prevalence: 4.32%). Some of the common blood borne viruses are human immunodeficiency virus (HIV) and hepatitis C virus (HCV).[16]

Concurrent fungal infections

Fungal co-infections are more common in COVID-19 patients admitted in the ICU.[10] They are a major cause of

mortality in mechanically ventilated COVID-19 patients.[17] A report in South Africa discusses fungal co-infections are common in COVID-19 patients. The most common fungal co-infections are caused by *Aspergillus fumigatus, Aspergillus flavus* and *Candida albicans, Candida tropicans*. [18]. Patients admitted with COVID-19 pneumonia may develop acute respiratory distress syndrome (ARDS) and become highly susceptible to invasive aspergillosis caused by *Aspergillus spp* leading to COVID-19 associated aspergillosis (CAPA), for which cases have been reported worldwide.[19-21] A narrative review reported a cohort of 43 patients, which identified 3 patients with candidemia. The common pathogens causing fungal co-infections were *Candida albicans, Candida tropicalis* and *Candida parapsilosis*. Furthermore, a retrospective study by Huges et al reported 3 fungal co-infections caused by *Candida albicans* in a cohort of 836 patients admitted with COVID-19. In addition to *Aspergillus* and *Candida spp*, fungal co-infections with *Pneumocystis jirovecii* and mycoses such as *Saccharomyces* have been reported in COVID-19 patients.[19,21]

Concurrent infections with tuberculosis

COVID-19 and pulmonary tuberculosis (PTB) has been reported as a co-infection in various studies.[19] A literature review discusses the co-infection of TB and COVID-19. Only 8 studies with a total of 80 patients were found. PTB causes Mycobacterium Tuberculosis in majority of the patients. COVID-19 and a TB co-infection was subdivided into groups based on different clinical scenarios including, TB diagnosed before COVID-19, TB diagnosed after COVID-19 and diagnosis of COVID-19 in patients receiving treatment for TB, were classified as COVID-19 with active TB. From 80 patients, 70 patients were reported as having active pulmonary TB during a diagnosis of COVID-19. A TB-COVID-19 infection was identified among both genders but predominantly males.[22] Diseases due to human immunodeficiency virus (HIV) and PTB lead to severe immunodeficiency and therefore, pose a higher risk of co-infections. TB is the leading cause of death in patients with HIV. The concurrence of TB, HIV and COVID-19 poses a major public health challenge, especially in endemic countries. Patients with COVID-19 increase the risk of TB and thus, makes diseased individuals highly susceptible to the causal nexus of HIV-TB-COVID-19.[23] A systematic review on different studies with COVID-19 and HIV/TB or only TB was conducted. A total of 21 studies were included in the systematic review, with 28,387 COVID-19 patients. Among them, 1294 were a co-infection of COVID-19 TB, whereas 1094 were COVID-19/HIV/TB. Occurrence of TB was also sub-grouped into previous TB and current TB. The previous TB group included patients where sputum was negative for acid fast bacilli and the diagnosis for TB was based on exposure to TB in the past, symptoms and radiograph images indicating active disease, whereas current TB was sputum smears positive for acid fast bacilli. According to the meta-analysis, current TB showed a strong risk of COVID-19 in HIV-infected cases OR 2.01 (95% CI 1.10–3.66), compared to uninfected HIV cases OR 1.30. TB occurrence pooled results between subgroup COVID-19/HIV/TB and COVID-19/TB was OR 1.67 (95% CI 1.06–2.65). The test for subgroup differences was not statistically significant. Therefore, the meta-analysis on the occurrence of TB among both groups of, COVID-19/HIV/TB and COVID-19/TB demonstrated that COVID-19 had a higher risk of occurring in current TB subgroup.[23]

Although sufficient literature is available on concurrent infections, but results of co-infections and super infections are often discussed cumulatively, thereby limiting correct interpretation. Many systematic reviews discussed occurrence of co-infections in SARS-CoV-2 in combination with other coronaviruses such as SARS-CoV and Middle East respiratory syndrome coronavirus (MERS-CoV), again limiting true interpretation of results on SARS-CoV-2 co-infections only. There is limited literature on the occurrence of COVID-19 as a co-infection with TB and HIV in and a lack of comparison with other microbial pathogens. Furthermore, studies on occurrence and prevalence of common concurrent infections are limited, as majority of the studies have different outcomes of interest such as clinical features, length of hospital stay, prognosis, status of mechanical ventilation, mortality and susceptibility to antibiotics. It is strongly recommended to discuss rates of co-infections and super infections in COVID-19 separately for a more precise understanding on occurrence and prevalence of microbial infections. Prospective studies on various microbiological pathogens causing co-infections in COVID-19 among various demographic variables such as age, gender, associated chronic co-morbidities and different hospital settings of **w**ards and ICU, including subgroups of patients with and without mechanical ventilation should also be considered.

CONCLUSION

The most common concurrent infection in patients with COVID-19 are bacterial co-infections followed by viral whereas fungal co-infection are the least common. Bacterial co-infections are caused predominantly by gram-negative organisms; however, they are only surpassed by *Staphylococcus aureus* which is the most common gram positive organism that causes bacterial co-infections. The most common viral co-infections are due to respiratory viruses such as influenza and respiratory syncytial virus. Fungal co-infections are most commonly found in COVID-19 patients admitted in the ICU. They are usually hospital acquired infections or superinfections and associated with increased mortality and morbidity. More research needs to be conducted on COVID-19 and concurrent infections with TB and HIV. Studies on microbial antibiotic susceptibility can steer antimicrobial stewardship programs and prove highly beneficial for improved outcomes in patients with COVID-19 and concurrent infections. A strong focus and clinical awareness should be placed on early diagnosis and

treatment of concurrent infection in COVID-19 to prevent adverse sequence of events.

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