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Update on the management of SARS-CoV-2 infection

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Respiratory co-and superinfections in COVID-19

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ABSTRACT

There are few publications on the impact of coinfection and superinfection in patients with COVID-19. Patients with higher severity are much more prone to secondary bacterial, fungal or viral infections. The overuse of antimicrobials in many viral infections (including SARS-CoV-2 infections) undoubtedly contributes to the current antimicrobial resistance crisis. In the context of COVID-19, we are witnessing an increase in multidrug-resistant bacterial infections in our hospitals. The heterogeneity of published studies makes it critical to perform more large-scale studies to better understand the pathogenesis of coinfections or superinfections in the COVID19 patient.

Keywords: COVID-19; SARS-CoV-2; antimicrobial resistance; coinfection, superinfection; Antimicrobial overuse

INTRODUCTION

Respiratory tract viral infections generate extraordinary morbidities and mortality rates worldwide, often in a seasonal way. In the last 20 years, we have witnessed four outbreaks of respiratory infections (i.e., SARS-CoV: 2002-2004; H1N1 Influenza: 2009–2010; MERS-CoV: 2012–2020; SARS-CoV-2: 2019-present). During the management of these outbreaks, the attention is firstly focused on the treatment of the viral infection itself and its complications, but it is mandatory to take into account the risk of existing coinfections and/or secondary infections that might develop in these patients. A relevant complication of viral respiratory infections is the potential colonization by other viral, bacteria or fungi, which might be associated with superinfection resulting in high morbidity, and mortality rates. The treatment for secondary bacterial infections is based on broad-spectrum antimicrobials, but this can result in undesirable side effects that undoubtedly have a negative impact on the host normal microbiota, or in other superinfections (e.g., *Clostridium difficile* or fungal infections).

According to the CDC, a superinfection is an infection following a previous infection while a coinfection is an infection concurrent with the initial infection. The difference is temporal: coinfections occur simultaneously, whereas superinfections develop following the initial infection. While the two terms are used interchangeably in medical literature and clinical practice, they are different clinical entities, being this particularly relevant when talking about COVID-19 patients. Superinfections and coinfections can enhance microbial pathogenesis, increasing the morbidity and mortality of viral infections.

THE VIRAL INTERFERENCE PHENOMENON

Epidemiological studies suggest that, following infection with influenza virus, there is a subsequent period of time during which the patient has a lower susceptibility to infection with other influenza viruses. This phenomenon (i.e., viral interference) appears to be independent of antigenic similarities between the viruses [1]. Viral coinfections may have different consequences. The most common is the above mentioned viral interference, where one virus competitively suppresses replication of the other. Interference between closely related viruses eventually results in elimination of the secondary coinfecting virus and is denoted as superinfection exclusion. The occasions where persistently infected cells withstand the challenge of a heterologous virus are termed superinfection suppression. Besides diminished viral replication (i.e., interference), coinfections with certain viruses may also trigger enhancement of the replication of one or both of the confecting viruses. In other cases, coinfection has no effect on the virus replication, and thus all the coinfecting viruses can coexist (i.e., accommoda-

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tion). Coinfection may modulate viral virulence and cell death, thereby altering disease severity and epidemiology. However, genetic recombination between coinfecting viruses depends on the similarity between the coinfecting viruses.

RESPIRATORY TRACT VIRAL-BACTERIAL SUPERINFECTION

The respiratory tract is susceptible to be colonized by environmental microorganism that circulate in the air. Barriers of the respiratory tract mucosal surface utilize a diversity of strategies to hinder microbe invasion. Physical barrier defenses include immunoglobulins, mucus, and beating cilia and separates the external environment from the internal host tissues [2]. However, pathogens such as *Streptococcus pneumoniae* target the respiratory tract causing severe damage to the host during their invasion. A classic example of viral-bacteria superinfection is the increased susceptibility of a patient with influenza infection to the acquisition of *Streptococcus pneumoniae*, resulting in a pneumonia that causes greater morbidity and mortality than infection with either pathogen alone. Different studies have shown that up to 65% of laboratory-confirmed cases of influenza infection are complicated by bacterial co/superinfections with the majority ranging between 11% and 35% in a meta-analysis [3]. The influenza A (H1N1) outbreak in 2009 had even developed into a global pandemic while causing seasonal flu epidemics each year. Secondary bacterial infections are one of the leading causes for influenza-associated deaths. The lethal synergism between influenza virus and *Streptococcus pneumoniae* strains accounts for the majority of diseases as well as mortality during influenza epidemics [3].

SARS-COV-1 AND COINFECTIONS/SUPERINFECTIONS

Severe Acute Respiratory Syndrome-related Coronavirus (SARS-CoV-1) was first report in Guangdong Province, China in November 2002. The diagnosis of bacterial co-infections was very high in these patients [4]. These included infections by methicillin resistant *Staphylococcus aureus*, *Klebsiella* spp., *Pseudomonas aeruginosa* or *S. pneumoniae*. Most SARS patients were treated with prophylactic broad-spectrum antimicrobials. Previous studies have shown that human metapneumovirus and other viruses can be also detected from SARS-CoV-1 patients.

MERS AND COINFECTIONS/SUPERINFECTIONS

The first cases of the Middle East respiratory syndrome (MERS) occurred in June 2012 in Saudi Arabia with later outbreaks observed in 2015 and 2018. Due to the high mortality rate of MERS infections, the impact of secondary bacterial infections remains unclear. Nosocomial bacterial pneumonia is however common among MERS patients with ventilator support.

SARS-COV-2 AND COINFECTIONS/SUPERINFECTIONS

Preliminary studies and some evidence from high-burden COVID-19 areas suggest that superinfections are common, particularly in severe cases. Almost all SARS-CoV-2 severe cases results in pneumonia with the inflamed alveolar space resulting an ideal environment for microbial growth [5]. The superinfecting pathogen may be bacteria, other virus or fungi. The presence of secondary bacterial infections in patients infected with SARS-CoV-2 complicates treatment and prognosis. Besides, the risk of superinfection with multidrug resistant bacteria challenges the treatment of severely sick COVID-19 patients in intensive care units.

A study described the incidence and predictive factors of secondary infections in a cohort study of patients hospitalized with COVID-19 at San Raffaele Hospital in Milan [6]. Among 731 patients, a secondary infection was diagnosed in 68 patients (9.3%); 22/731 patients (3%) had at least one respiratory tract infection. The overall 28-day cumulative incidence of secondary infections was 16.4%. Lower tract respiratory infections were caused mainly by Gram-negative pathogens (14/26, 53.8%). Eleven patients were diagnosed with putative invasive aspergillosis. At multivariable analysis, early need for ICU, respiratory failure, and severe lymphopenia were identified as risk factors for the development of secondary infections. In a multicenter study [7]. in China that included 476 COVID-19 patients, secondary bacterial infections were significantly associated with outcome severity. Patients were divided into 3 groups (i.e., moderately ill, severely ill, and critically ill). The critically ill patients had the highest percentage of secondary bacterial infections (34.5%) compared to patients in the moderately ill and severely ill groups (3.9% and 8.3%, respectively). Severe COVID-19 is associated with intensive care unit admission, increased secondary infection rate, and significant worsened prognosis.

Risk factors for secondary infections in severe COVID-19 have not been fully described. A study including critical COVID-19 patients from Shanghai found 57% patients who developed secondary infections [8]. The most common infection site was the respiratory tract. The most frequent pathogens were gram-negative bacteria (50%), followed by gram-positive bacteria (26%), virus (11%), and fungi (7%). Patients receiving invasive mechanical ventilation had a higher risk of secondary infections. Respiratory Infection rate post high flow, tracheal intubation, and tracheotomy were 12%, 30%, and 92%, respectively. Secondary infections led to lower discharge rate and higher mortality rate. Diagnosis of secondary bacterial infections typically requires testing of samples obtained by sputum expectoration/induction, nasopharyngeal/oropharyngeal swabs of respiratory passages, bronchoscopy, thoracentesis, and/or lung tissue biopsy. Conventional diagnostic tests have poor sensitivity in identifying the etiologic organisms responsible for respiratory infections. A study used real-time PCR to detect specific pathogens causing COVID-19 coinfections [9]. They found that 243 (94.2%) patients were coinfected with

at least one of 39 different pathogens. Culture accompanied with metagenomics sequencing increased pathogen diagnostic rate. Bacterial coinfections were predominant (91.8%) over viral (31.5%) and fungal (23.3%) infections. Although this study found no significant association between coinfection rates and outcome severity or mortality, they described interesting coinfection patterns in different clinical groups

COVID-19 AND INCIDENCE OF COMMUNITY-ACQUIRED PNEUMONIA

The impact of the COVID-19 pandemic on the incidence of community-acquired pneumonia is not well defined. One study compared the number of elderly patients admitted to a hospital for community-acquired pneumonia from January to June 2020 with the numbers for the same period in each of the last three years [10]. The number of patients diagnosed with community-acquired pneumonia began to decline in February 2020, and by April 2020 the number was significantly lower than in the same period of the previous three years. There is no evidence on the impact of general infection control measures, such as the use of facemasks or hand washing, on the development of community-acquired pneumonia. However, these measures might have indirectly contributed to reducing the number of cases by preventing common viral infections that could be a trigger for community-acquired pneumonia.

CONCLUSIONS

Data regarding superinfections/coinfections in COVID-19 patients are limited and still emerging. The relatively high incidence of severe infection and mortality in COVID-19 is thought to be in part due to secondary infections, alongside with lack of natural immunity and viral replication in the lower respiratory tract leading to severe lung injury and acute respiratory distress syndrome. We have few detailed clinical studies on co-or superinfections occurring in COVID-19 patients. Since mortality rates from antibiotic-resistant bacterial infections are increasing worldwide, and the numbers of COVID-19 patients are steadily increasing it is critical to analyze this point in detail. The use of broad-spectrum antibiotics is often a routine preventive measure in these patients. Until programs to optimize antibiotic use in these patients are implemented in our hospitals, antibiotic overuse will continue to be unavoidable, impacting the genesis of multidrug-resistance phenomena.

Coronavirus infections are and will likely be a clinical challenge for many years to come. Pandemics due to coronaviruses and other emerging pathogens are inevitable in a globalized world with interconnected societies, travel and commerce. We should invest in being better prepared for the next pandemic by exploring and establishing new pathways to treat pathogens implicated in coinfections and superinfections to avoid deepening the health crisis due to antibiotic resistance.

CONFLICTS OF INTEREST

The author declares no conflicts of interest.

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