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Update in SARS-CoV-2 pneumonia

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Respiratory infections in Coronavirus disease 2019

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ABSTRACT

In the last two years, the capacity of our hospitals has clearly been overwhelmed due to the COVID-19 pandemic The patient who comes to the hospital with a respiratory coinfection does not have the same characteristics as the patient who suffers a superinfection while hospitalized. The number of secondary infections increase proportionally to the severity of the patient's disease. Besides, pathogens that cause a coinfection are clearly differentiated from the pathogens that cause a superinfection. However, in patients subjected to airway manipulation, superinfections by distinct pathogens can occur. Seventy five percent of patients admitted worldwide with COVID-19 (especially during the first two waves of the pandemic) received some form of antibiotic treatment during admission. In this context, it is essential to develop and implement algorithms that allow us to define the predictors in each individual case for the development of a superinfection

Key words: Coronavirus disease 2019; Coinfection; Superinfection; Rational antimicrobial use

INTRODUCTION

In the last two years, the capacity of our hospitals has clearly been overwhelmed due to the COVID-19 pandemic. This has meant that inpatient care has changed dramatically. The increase in the number of patients hospitalized with pneumonia caused by SARS-CoV-2, together with the comorbidities that these patients present, has clearly increased the risk of suffering a superinfection during admission [1]. Most of the published literature does not distinguish between COVID-19 patients with a coinfection or a superinfection. According to the CDC definitions, the difference between both entities lies in their temporality. A coinfection is an infection that appears concurrently with SARS-CoV-2 infection, while a superinfection is one that occurs days later in a patient diagnosed with COVID-19. In other words, the difference between the two entities is temporal and this fact has implications that are important from a diagnostic and therapeutic point of view [2].

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PATHOPHYSIOLOGY OF SUPERINFECTION IN COVID-19

The primary function of the respiratory system of gas exchange renders it vulnerable to environmental pathogens that circulate in the air. Physical and cellular barriers of the respiratory tract mucosal surface utilize a variety of strategies to obstruct microbe entry. It is well known that certain respiratory infections caused by viruses, such as influenza virus infection, eventually damage the respiratory epithelium and result in decreased mucociliary clearance, increased bacterial receptor cell surface area, and intercellular junction incompetence. These facts, combined with an impaired immune response due to the functional damage of macrophages and neutrophils, together with a deregulated cytokine response, produce a modification of the microenvironment that ends up creating a perfect niche for secondary infections [3]. In the case of influenza, secondary bacterial pneumonias caused by *Streptococcus pneumoniae* or *Staphylococcus aureus* are well described in the literature.

Several reviews have evaluated the pathophysiology of coinfection in patients diagnosed with SARS-CoV-2 pneumonia [4]. In this regard, we can distinguish two periods in the pathogenesis of SARS-CoV-2 pneumonia. In the initial stages of pneumonia, infection of bronchial epithelial cells and type I and II alveolar pneumocytes, as well as infection of capillary endothelial cells occurs. This is followed by a local inflammatory response with recruitment of lymphocytes, monocytes, neutrophils, and macrophages. This cytological response is accompanied by a massive release of cytokines that triggers the

second phase in SARS-CoV-2 pneumonia. In this second phase, because of a continued inflammatory response, there is thickening of the alveolar-capillary space, with increased vascular permeability leading to the formation of hyaline membranes. At the endothelial level, coagulation is activated leading to microthrombus formation and other phenomena related to thrombo-inflammation. All these factors contribute to create a perfect microenvironment that leaves the pulmonary alveolus in a perfect situation for other pathogens invasion, whether viral, bacterial or fungal, to adhere to this damaged alveolar epithelium, multiply and generate a secondary infection [5].

SUPERINFECTION BURDEN IN COVID-19

A recently published study analyzes the risk factors and characteristics of infections occurring in critically ill patients diagnosed with COVID-19 [6]. This study does not differentiate between coinfection and superinfection. Thirty-eight patients were included, 58% of whom developed a secondary infection, with respiratory infections being the most frequent, followed by bacteremia and urinary tract infections. According to a meta-analysis published by Langford, where a distinction is made between coinfections and superinfections, 3.5% of patients admitted due to COVID-19 suffer a bacterial coinfection, with 14.3% of patients suffering a bacterial superinfection during admission [7]. In a multicenter study published by Feng [8], the number of secondary infections increased proportionally to the severity of the patient's disease. In this study, 4% of patients with moderate disease, 8.3% of patients with severe disease, and up to 34% of critical patients are diagnosed with a superinfection during admission.

Regarding to the etiology of these infections, Westblade et al. showed that pathogens that cause a coinfection are clearly differentiated from the bacterial pathogens that cause a superinfection [9]. Bacterial coinfections are dominated by community pathogens such as *S. pneumoniae* or *Haemophilus influenzae*, while superinfections occurring after admission are dominated by hospital pathogens such as enterococci, *Pseudomonas aeruginosa*, *S.s aureus* and *Enterobacter* species. The pathogens most frequently isolated in a study [6] were Gram-negative bacilli in 50%, followed by Gram-positive cocci in 25%. It should be noted that 11% of patients had a secondary viral infection and almost 8% had a secondary fungal infection. These secondary infections were associated with an increase in the average length of stay and in the mortality rate. Interestingly, in this study, the rate of respiratory infections was 90% in patients undergoing tracheotomy, 30% in patients undergoing mechanical ventilation and 12% in patients undergoing non-invasive mechanical ventilation techniques.

It should be considered that sometimes, and especially in patients subjected to airway manipulation, superinfections by distinct pathogens can occur. In a paper published by Zhang et al [6] in which they study the time of appearance of secondary respiratory infections after different types of respiratory support, they describe how after a tracheotomy the mean time until the appearance of a superinfection is 9 days, with a range of 31 different pathogens being observed in this type of infection. After tracheal intubation, the mean time to the appearance of an infection was 4.5 days, with a smaller range of pathogens, and the mean time to the appearance of a secondary superinfection after the use of noninvasive ventilator support, the mean time was 7.5 days, with a lower diversity of pathogens than in the other 2 situations.

As it has been described in several studies, patients with COVID-19 pneumonia are patients at special risk of suffering secondary invasive fungal infections, as occurs in the case of other viral pneumonias such as pneumonias caused by the influenza virus [10]. Patients with COVID-19 pneumonia, especially those patients in critical care units, and who have undergone treatment with corticosteroids and other immunosuppressants such as interleukin inhibitors, and have also undergone broad-spectrum antibiotic treatment, are patients who are particularly predisposed to fungal superinfection, especially by *Aspergillus* species or, as has been described in some countries, by *Mucor* species.

RISK FACTORS AND IMPACT OF SUPERINFECTIONS

Several studies have evaluated the risk factors that predispose to a superinfection in patients with COVID-19 pneumonia. In the study by Ripa et al. for example, the longer the duration of hospitalization, the greater the probability of superinfection [11] The percentage of patients who suffer a superinfection after 7 days of admission is 2%, while in patients with stays of 29 days, the percentage of infections rises to 16%. The absolute number of lymphocytes is another factor that has been described in several studies as a predictor of secondary superinfection. The patients at greatest risk would be those with counts below 0.7×10^9/L. In patients subjected to mechanical ventilation, PaO2/FiO2 < 200 is a well-established risk factor for secondary superinfection. Regarding the impact of these superinfections on the patient's evolution and average length of stay, it has been well demonstrated that patients who suffer a superinfection during the course of COVID-19 significantly prolong their average length of stay when compared to those who do not suffer a secondary infection, and are also more likely to die than those who do not have a secondary infection [6].

COVID-19 AND ANTIMICROBIAL USE

Langford's meta-analysis, described how 74% of patients admitted worldwide (especially during the first two waves of the pandemic) with COVID-19 received some form of antibiotic treatment during admission [12]. These figures were very stable across WHO regions. If we stratify patients by age, up to 83% of adults received antibiotic treatment during admission, while only 40% of children do. Similarly, if we stratify by place of patient care, up to 86% of patients admitted to the ICU received antibiotic treatment at some time during admission, 74% of patients admitted to a conventional hospital ward received antibiotic treatment and, surprisingly, up to 60% of

patients treated on an outpatient basis received some type of antibiotic treatment. In this same meta-analysis and for the different WHO regions, the most used families of antibiotics were quinolones, and macrolides, followed by beta-lactams combined with beta-lactamase inhibitors and cephalosporins. In this context, we must consider the impact that antimicrobial therapy in these patients has on the microbiota (especially of the gastrointestinal tract). In this sense, there is some work such as that of Zuo, which describes how the dysbiosis caused by antibiotics in COVID-19 patients impacts on the immune response at the lungs, generating a worse respiratory evolution of these patients [13].

In this context, it is essential to develop and implement algorithms that allow us to define the predictors in each individual case for the development of a superinfection for two reasons. The first is to decide in which patients it is prudent to initiate empirical antibiotic treatment because they have a high risk of superinfection, as well as in which patients it is not necessary to initiate preventive antibiotic treatment because they have a low risk of superinfection. In any case, it is necessary to establish good diagnostic protocols, including the possibility of screening for multidrug-resistant bacteria in certain patients to be able to choose the right empirical treatment in case of suspected superinfection. It is equally important to define in which patients' antimicrobials should be used and in which ones an antimicrobial treatment is not indicated. Similarly, it is essential to re-evaluate each patient 48-72 hours after admission, from the point of view of secondary infection, to decide whether it is necessary to continue with antibiotic treatment in patients in whom antibiotic treatment has been started or whether it can be stopped

REMAINING QUESTIONS

- Which clinical features and laboratory tests can reliably identify the small proportion of hospitalized patients with COVID-19 who have bacterial coinfection and who therefore should undergo diagnostic testing for other infections and receive empirical antibacterial therapy?
- Will the prevalence of bacterial coinfection upon hospital admission for COVID-19 change in subsequent waves of the pandemic, particularly with the emergence of new SARS-CoV-2 variants?
- How will the routine use of corticosteroids change the spectrum of hospital acquired bacterial infections in patients requiring prolonged hospitalization for COVID-19?
- How will the increase in COVID-19 patients who require intensive care around the world influence the emergence of multidrug-resistant bacterial infections?

CONFLICTS OF INTEREST

Author declares no conflicts of interest

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