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Editorial

Coinfection and superinfection in SARS-CoV-2 pneumonia. Two underestimated threats. The need of empirical treatment under debate

Coinfección y superinfección en neumonía por SARS-CoV-2. Dos amenazas infraestimadas. La necesidad de tratamiento empírico a debate

Unfortunately, infections have become one of the main complications of patients with severe SARS-CoV-2 pneumonia, specially in critical care setting. Furthermore, these infections are associated themselves to and increased morbility and a worse prognosis without any doubt. Moreover, it is going without saying than some conditions such frequent development of organic failure requiring invasive supportive treatments, poor immune status and prolonged ICU length of stay in saturated structural areas of patients are risk factors for nosocomial infection development.[1,2]

In this issue, two interesting studies have been published in this field. One of them[3] is related to the incidence of coinfections and superinfections of patients with severe SARS-CoV-2 pneumonia in a general hospital in Spain, their clinical and microbiological features and their prognosis. The second one[4] analyzes the influence of COVID infections in the rate of blood cultures extracted-including contamination ratio- (before and after design), and their etiology also in our country. Both manuscripts actualize this relevant information and clearly resolve these important matters.

In the first of them Nebreda-Mayoral et al.[2] performed a retrospective observational study of all patients admitted for COVID-19 and bacterial/fungal infections at the Hospital Clínico Universitario of Valladolid in Spain during a period of three months in the first wave. The authors included 712 COVID-19 patients (44% of them were admitted in ICU). Sixteen of them presented bacterial/fungal coinfections or superinfections. Coinfections were diagnosed in 5% whereas superinfections were detected in 11%, majority were admitted in ICU. Most common pathogens of respiratory coinfection were *Streptococcus pneumoniae* (6) and *Staphylococcus aureus* and urinary track infection was the main foci. *Acinetobacter baumannii* multidrug-resistant was the main agent of superinfections due to an outbreak in ICU. Only three patients were considered to have probable pulmonary aspergillosis. The outbreak of *A. baumannii* was a determining factor in the increases of the incidence of infection and the mortality of ICU patients.

These data shows similarities and differences with other studies recently published. As the authors comment, the incidence of coinfection and superinfections depend on the population studied. In this way Langford et al.[5] evaluated the presence of bacterial coinfection in a large meta-analysis of over 3338 patients. A total of 3.5% of the patients presented coinfection. In contrast in relation to the critically ill setting, the authors analyzed the data of 5 studies documenting coinfection in 14 out of a total of 144 patients (9.7%). In other large metanalysis published by Lansbury et al.[6] described an higher number of coinfections in ICU patients than patients in mixed ward/ICU settings (14% versus 4%). The etiology of coinfections in these two large metaanalysis[5,6] seems to be similar to those described in the manuscript from Valladolid[2] being *S.pneumoniae*, *S.aureus* and *H. influenzae* the most frequent isolated microorganisms. As remarkable additional data the pooled proportion with a viral co-infection was 3% described by Lansbury el al.[6] with Respiratory Syncytial Virus and influenza A the commonest. These data have been also corroborated by a Spanish study performed in the first wave.[7]

Although A. *baumanni* outbreaks[8] has been rarely reported during the pandemia in ICU as Nebreda-Mayoral et al do, major differences are found when reviewing ICU nosocomial infection reported data, specially about incidence and etiology. The first data generated by the ENVIN-COVID registry[9] during the first wave including 1525 patients with COVID-19 admitted to intensive care, showed that 50% of the patients had suffered one or more infections, with multiplied ratio between two- and four-fold for the infections under surveillance. Two Spanish ICU[10,11] also have noticed an incidence of almost 52% referred to infections acquired in the ICU. Respiratory foci were the most common presentation and *Pseudomonas aeruginosa* was the most frequently isolated microorganism in these last three studies instead of *A. baumanni*.

The role of difficult to treat microorganism has been also analyzed in ICU. In a multicenter study carried out in 36 ICUs in Europe,[12] which included the same number of patients on mechanical ventilation per center with SARS-CoV-2 infection, influenza infection or no viral infection, the incidence of ventilator-associated tracheobronchitis and ventilator associated pneumonia was greater in the patients with SARS-CoV-2 than in the other two groups. Gramnegative bacilli such as *P. aeruginosa*, *Enterobacter* spp. and *Klebsiella* spp. were responsible for most of the episodes in all three study groups. Surprisingly, the percentage of patients with

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episodes involving multiresistant bacteria was lower in pneumonia due to SARS-CoV-2 than in the other two groups.

The Nebreda-Mayoral study[2] failed to demonstrate an elevated incidence of *Aspergillus* infection in these patients, however it is well known (especially after the first wave) that the incidence can reach in same studies at 30%. This is the reason, among others, to the development of CAPA (COVID-19-associated pulmonary aspergillosis) new definitions.[13]

The relationship between the use of tocilizumab and increased rate of superinfections has not been resolved in the work from Valladolid either and its role remains controversial. Somers et al.[14] evidenced that the use of tocilizumab in a cohort of 154 patients subjected to mechanical ventilation was associated to a greater proportion of superinfections (54% versus 26%) without any significant influence on mortality (22% vs 15%) being pneumonia (45%) and bacteremia (14%) the most frequent conditions. However, in the largest meta-analysis to date, Tleyjeh et al.[15] found the use of tocilizumab to imply no higher nosocomial infection rate than in the control group. A new well-designed study focused on superinfections in critically ill patients and the use of tocilizumab is warranted to resolve this controversy.

In the second manuscript[4] the authors investigated the rate and etiology of bacteremia and contaminated blood cultures collected from COVID and non-COVID patients. They also performed a retrospective analysis in a tertiary hospital in Spain during the COVID first wave. There were a 22.7% and 18.8% of decrease of number of blood cultures obtained compared to previous years. However, the rate of bacteremia was 1.2% higher among COVID-patients than among non-COVID patients. COVID patients had a higher proportion of nosocomial bacteremia (95.5%) than non-COVID patients (30.5%) In COVID-positive patients, the contamination rate was higher (12.3% vs 5.7%) than in non-COVID patients.

A large study performed in New York city[16] showed opposite results regarding the rates of bacteriemia found. In this study this was significantly lower among COVID-19 patients (3.8%) than among COVID-19-negative patients (8.0%) and those not tested (7.1%). One possible explanation must be related with a minor rate of contamination because the proportion of positive blood cultures that yielded contaminants was also significantly higher among COVID-19 patients.

Two important facts must be noticed after reading this manuscript, the first one is about the decreased number of blood cultures obtained. We are sure this fact is due to the difficulty that isolation and physical barriers in COVID infection add to obtain samples. The second one is related to the high proportion of blood culture contamination was identified, especially in COVID-positive patients. As the authors remarks It could be explained by unfamiliarity of additional personal protective equipment worn by healthcare workers taking blood cultures. In contrast, as Dagere S[17] et al. recommends, the accurate differentiation of a contaminant from a true pathogen relies on a multidisciplinary approach and the clinical judgement of experienced practitioners.

Finally, after considering the results of the two studies published in this issue, a debate arises about the need or not of empirical treatment in these two entities-coinfection and superinfections.

In the case of coinfections certainly not as a general rule. Following the recommendations of SEMICYUC[18] in critical care setting we should recommend early empirical treatment of possible bacterial pulmonary coinfection (strong clinical suspicion, purulent secretions, biomarker elevation and/or positive antigens) upon admission to the ICU of patients with COVID-19, since such coinfection is associated to increased mortality. The early suspension of antimicrobial treatment once coinfection is ruled out must be a reality in clinical practice.

We also suggest an early diagnostic strategy and empirical treatment, in view of the high risk of bacterial and fungal superinfection in patients with COVID-19 specially subjected to mechanical ventilation.

The mission of the clinician is to promote rational, efficient and safe use of antibiotics, by means of scientific evaluation and selection of the right antimicrobial for each patient based on criteria of effectiveness, safety, quality and efficiency, based on risk factors and local flora. Then we must hit at the first attempt with appropriate empirical treatment and after, if possible, deescalate.

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