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CHEST

The Elephant in the Room

Secondary Infections and Antimicrobial Use in Patients With COVID-19

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COVID-19 forced the medical community to face unprecedented challenges. Caught in the middle of a pandemic, clinicians and researchers struggled to produce high-quality data able to guide the management of this new disease.[1] In this context, the study from Grasselli et al[2] in this issue of *CHEST* is a virtuous example of a collaborative effort aimed to elucidate clinical features and outcomes of a large cohort of patients. The authors took advantage of a multicentric ICU network to prospectively collect clinical and microbiological data on >700 subjects with severe COVID-19 from the first pandemic wave. In the current article, the authors retrospectively describe the incidence, risk factors, microbiologic landscape, and clinical impact of secondary infections that occurred at or after ICU admission.

Men and women with COVID-19, especially if hospitalized in the ICU, have been reported to be prone to secondary infections, either from bacterial or fungal pathogens.[3,4] Indeed, in their analysis the authors highlight how almost one-half of the patients experienced a hospital-acquired infection, ventilator-associated pneumonia being the most frequent.[2] Of note, approximately one-third of all the infectious episodes were due to multidrug-resistant organisms (MDROs).

The considerable burden of infectious complications in this population necessitates additional awareness on the appropriate use of antimicrobial drugs. Previous reports have suggested that a substantial proportion of subjects with COVID-19 were treated with antibiotics at admission or within the first days of hospitalization.[5,6] Current guidelines are ambiguous regarding the use of empiric antibiotic therapy in severely ill patients with SARS-CoV-2 infection. In this regard, the work by Grasselli et al[2] gives significant guidance to assist physicians facing this scenario. The authors report that, despite 68% of patients receiving antibiotics at the time of ICU admission, after a multisite routine diagnostic workup, a documented secondary infection was observed in only 1% of subjects, which confirms previous observations.[3] These findings suggest that antibiotic therapy could be withheld with limited risks in a considerable fraction of patients with COVID-19, even when severely ill, if recently hospitalized and without evidence of co-infection. This would prevent the instauration of a vicious circle of antibiotic misuse, increased prevalence of MDRO colonization and infection, and subsequent initiation of broad-spectrum antimicrobials, with deleterious consequences on individual patients and global ecology. Even if a possible benefit of ongoing broad-spectrum antibiotic therapy on the development of secondary infections during ICU stay was suggested by the multivariate statistical analysis, this finding seems to be spurious, given the local epidemiologic conditions and the resistance profile of the documented microbiologic isolates. Moreover, the use of broad-spectrum antimicrobials may have undermined the diagnostic yield of microbiologic investigations, thereby potentially leading to underdiagnosis of subsequent secondary infections.

Although the burden of co-infections at the onset of the disease seems to be negligible, the proportion of patients who experience secondary infections during ICU stay is notably higher compared with that of historic cohorts that describe patients without COVID-19 who are admitted to the ICU.[5,6] Furthermore, the high prevalence of infections due to MDROs reported in the study by Grasselli et al,[2] even in the context of the local

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epidemiology, is worrisome but sadly not unexpected, given the widespread use of empiric antimicrobials and the ICU strain experienced during this pandemic, conceivably leading to substandard adoption of infection control measures.

To emphasize the delicate equilibrium in the management of antimicrobial therapies, sepsis and septic shock contributed consistently to morbidity and death of patients with COVID-19 from this cohort.[2] Sepsis is a time-dependent process, and the underlying pathologic alterations in the immune network may not be counteracted by antimicrobial therapy after a certain time threshold.[7] Establishing the cause of clinical deterioration and sepsis in COVID-19 is challenging, because SARS-CoV-2 infection may lead to a so-called viral sepsis,[8] a condition that shares many features with sepsis caused by other microorganisms, and is frequently clinically indistinguishable. Given the absence of reliable biomarkers able to predict the cause of clinical worsening, the decision to initiate antimicrobials is delegated to the sensitivity of the treating physician. In this context, maintaining a low selective antimicrobial pressure is the best available option to ensure the timely initiation of an effective antibiotic therapy. It seems crucial to develop tools to identify phenotypes associated with sepsis due to SARS-CoV-2 infection, because the treatment of these patients should be drastically different from that of sepsis secondary to hospital-acquired infections.

A final consideration has to be made on the impact of immune-modulating therapies on COVID-19. The use of agents able to temper the over-activation of the immune system during SARS-CoV-2 infection, especially corticosteroids, has been associated consistently with a decrease in morbidity and mortality rates.[9,10] However, the possible development of iatrogenic immune suppression and, consequently, the enhanced susceptibility to infectious complications must be taken into account in the decision to initiate such therapies. In the current study, the authors did not find a strong signal linked to a possible increased incidence of secondary infections in patients treated with immune-modulating agents.[2] Even though this finding must not lead to an indiscriminate, and likely deleterious, liberal use of these drugs, it reinforces the idea that, in severely ill patients with COVID-19, the administration of immune-modulating agents (especially corticosteroids and tocilizumab that already are linked to a decrease in mortality rates) likely outweighs the risk of secondary infections.

In the absence of highly effective antiviral therapies, COVID-19 put the medical community in the position of treating the effects of a disease, rather than its cause. With the hope that vaccinations and other mitigation strategies would reduce the population susceptibility to severe COVID-19 and that newer, more effective antiviral treatments would provide weapons to counteract the disease, every research effort has to be made to help physicians to provide the best supportive care to patients affected by COVID-19. In this context, studies like the one from Grasselli et al[2] are much-needed insights to improve the current management of treatable conditions linked to adverse outcomes.

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