



Use of antibiotics in respiratory viral infections

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Besides the intrinsic complications caused by SARS-CoV-2 infection, other conditions, such as bacterial infections pose an additional risk to COVID-19 patients. The study published in this issue by Moreno-Torres et al. [1] assessed the rate and predictors of bacterial infections in patients consecutively admitted with COVID-19 to a tertiary hospital in Madrid, Spain, during the first wave of COVID-19. Among 1594 hospitalized patients with COVID-19, 135 (8.5%) experienced bacterial infectious events, distributed as follows: urinary tract infections (32.6%), bacteremia (31.9%), pneumonia (31.8%), intra-abdominal infections (6.7%) and skin and soft tissue infections (6.7%). Independent predictors of bacterial infections were older age, neurological disease, prior immunosuppression, and admission to intensive care units (ICU).

The mortality rate was significantly higher in COVID-19 patients with bacterial infections than in the rest (25% vs 6.7%, respectively; $p < 0.001$). However, in multivariate analysis, older age, prior neurological or kidney disease, immunosuppression and acute respiratory distress syndrome (ARDS) were associated with increased mortality ($p < 0.05$), while bacterial infections were not. On the other hand, the use of steroids or steroids plus tocilizumab did not confer a higher risk of bacterial infections while increased survival rates. In summary, the authors concluded that baseline COVID-19 severity rather than incident bacterial infections contributed to mortality. Thus, rather than considering empiric antibiotic therapy, the use of steroids or steroids plus tocilizumab might improve survival in this population.

From a physio-pathological standpoint, two consecutive phases can be distinguished during acute SARS-CoV-2 infection. The first extends for 7–10 days and results from viral replication in the upper respiratory tract alongside with influenza-like symptoms, such as cough, fever, headache and myalgia. The second phase results from the host immune response mostly in the lungs around 10–14 days later [2]. The presence of lung interstitial infiltrates in image testing at this stage is very common. The severity of hypoxemia reflects the extent of the alveolar inflammatory reaction. In older individuals, the immune response is more prone to be dysfunctional, accompanied by a cytokine release syndrome ('cytokine storm') that can be life-threatening.

According to this stratification into two phases for COVID-19, antiviral strategies have been postulated for content the first phase, whereas anti-inflammatory agents have been recommended to ameliorate the second phase. Antiviral molecules such as remdesivir or specific monoclonal antibodies have been tested with limited success [3]. Steroids, namely dexamethasone, have shown to reduce the severity of SARS-CoV-2 pneumonitis and improve survival. Indeed, they are the cornerstone of treatment for moderate-to-severe COVID-19.

Data regarding the rate of superinfections in COVID-19 patients remain scarce, despite the relevance of using efficacious therapies for these conditions, as well as the potential impact of antimicrobial treatments on survival in this population. Retrospective data from several cohorts estimate the incidence of bacterial superinfections between 5 and 27% or 13.5–44% in COVID-19 patients requiring ICU admission [4]. These studies concur to highlight that respiratory and urinary infections are the most frequent bacterial co-infections in COVID-19 patients. Arguably, admission to ICU is associated with other, more complex infections, such as ventilator-associated pneumonia and bloodstream or urinary tract infections [5]. Furthermore, nosocomial infections tend to be associated with more resistant bacterial strains, including *C. difficile* [6], requiring the use of broad-spectrum antibiotics, which pose additional challenges. Outside ICUs, the

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use of empiric antibiotic therapy has not proven any benefit on SARS-CoV-2 outcomes [7].

Other inflammatory lung infections result in long-lasting immunosuppressive effects, somewhat resembling the T cell exhaustion and immune paralysis that occur in sepsis [8, 9]. As shown by Moreno-Torres et al. [1], severe inflammatory responses driving to ARDS in COVID-19 patients lead to poor clinical outcomes. This is not only the result from respiratory failure but from the need to require invasive ventilation, with the added risk of developing ventilator-associated pneumonia and other nosocomial infections [10]. Although the use of monoclonal antibodies, such as tocilizumab, has been associated with reduced mortality in patients with moderate-to-severe SARS-CoV-2 pneumonitis, these agents may increase the rate of bacterial superinfections [11]. In this regard, antibiotics might be a good companion in this subset of patients.

Finding a cure for SARS-CoV-2 infection remains a major goal of basic and clinical research. In the mean time, improvements in the management of COVID-19-associated complications, such as bacterial superinfections, will be much appreciated. Despite the relatively low incidence of bacterial infections, the use of antibiotics may benefit the subset of COVID-19 patients requiring ICU admission and mechanic ventilation as well as those under immunotherapy with monoclonal antibodies. Arguably, the early identification of bacterial infections in this subset of patients along with prompt antibiotic therapy might be crucial for decreasing current COVID-19 mortality.

Declarations

Conflict of interest All authors acknowledge no conflicts of interest relevant to this article.

Human and animal rights statement This commentary is the original work of the named authors, who reviewed previously published information. No new human or animal studies were performed by the authors.

Informed consent For this type of study, no informed consent is required.

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