Archivos de Bronconeumología 58 (2022) 208–210

Sociedad Española de Neumología y Cirugía Torácica SEPAR

ARCHIVOS DE Bronconeumología

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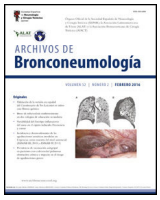

Editorial

What's Next in Pneumonia?

¿Qué nos depara el futuro de la neumonía?

Pneumonia remains the leading infectious cause of death for all ages worldwide.[1] Due to the progressively aging population globally, the proportion of very old patients (VOP ≥ 80 years) hospitalized with pneumonia continues to rise; similarly, the proportion of VOP requiring treatment in intensive care units (ICU) is increasing.[2] VOP are at a high risk of pneumonia due to multiple chronic comorbidities, immunosenescence, malnutrition, frailty and polypharmacy. This same group also faces a higher likelihood of severe pneumonia and mortality.[3] Conversely, pneumonia disproportionately affects children under five years old. In 2019, the respiratory disease claimed the lives of 672,000 children aged less than five years.[1] This means that a child who has not even turned five years old will die every 47 s due to pneumonia.[1] No doubt remains that pneumonia is a major burden on global health. Yet, despite that, there are still several challenges and controversies related to critical aspects of pneumonia management and prevention.

Early-risk severity stratification and appropriate antimicrobial therapy have been well-established to be integral components in improving pneumonia outcomes. However, there are no risk stratification tools to guide management of pneumonia in VOP and children requiring intensive care. The most widely used severity scores, like PSI and CURB65, perform well in predicting 30-day mortality; however, these same scores fall short when it comes to predicting the need for ICU admission. The first upcoming challenge in pneumonia will be to continue research that demonstrates the usefulness of severity scores in predicting which patients would benefit from more aggressive treatments and ICU care.

Additionally, early identification of pneumonia-causing microorganisms is essential in implementing adequate antimicrobial therapy. Indeed, a patient's prognosis could benefit significantly from adequate microbial treatment.[4] However, we can only identify the microbial cause of pneumonia in approximately 50% of cases. While a detection of specific pathogens such as respiratory viruses have improved via the application of molecular techniques,[5] more must be done. The lack of standardization of these techniques limits their full integration in clinical practice. Additionally, result interpretation can be ambiguous with respect to pathogen detection and colonization/infection determination. As the current COVID-19 pandemic has demonstrated, the role of molecular tests in detecting pathogens, including emergent viruses like severe acute respiratory syndrome coronavirus 2 (SAR-CoV-2), is becoming more pivotal.

In the coming years, a second challenge of pneumonia research will be to evaluate the usefulness, applicability and standardization of molecular testing in detecting pneumonia pathogens and related resistance to improve and personalize the management and care for patients with community-acquired pneumonia (CAP). Currently, *Streptococcus pneumoniae* and influenza virus are the most common causes of pneumonia. Although multidrug-resistant (MDR) pathogens present in a lower proportion in CAP, especially in severe cases, the impact of such microbes on clinical outcomes is huge.[5,6] It will therefore be important to continue research also on the utility of scores that predict patients at risk of drug-resistant microorganisms like PES pathogens (*Pseudomonas aeruginosa*, extended-spectrum β-lactamase-producing *Enterobacterales*, and methicillin-resistant *Staphylococcus aureus*) that recently have emerged as causes of CAP.[6,7]

In the last ten years, scores assessing the potential risk of MDR pathogens in patients with CAP have come into development.[8–11] However, the scores present a higher variability on the assigned weight to each variable investigated, and variability in the thresholds for patients at risk of MDR pathogens is present. Interestingly, the PES score[7] has showed a high negative predictive value (98%), making it possibly an important tool to rule out patients with CAP who do not need antibiotic coverage against PES pathogens. However, future studies are needed to support the therapeutic clinical decision-making processes, especially as it relates to cases caused by MDR pathogens others than PES microorganism. For example, carbapenem-resistant *Enterobacterales* or *Acinetobacter baumanni* are MDR pathogens that are associated with higher morbidity and mortality despite low frequency of such microorganisms in this series of patients.[12–14]

At the same time, mounting evidence supports considering the immunological profile of patients with CAP as a useful tool in assessing severity and prognosis in pneumonia.[15,16] Researchers have found that the lymphopenic CAP (L-CAP) phenotype was associated to increased severity, mortality and a dysregulated immunological response in patients with CAP.[15,17] In patients with CAP and sepsis, lymphopenia was also reported to be associated with an increased risk of ICU admission and 30-day mortality.[18] The neutrophil-to-lymphocyte ratio (NLR) and C-reactive protein-to-lymphocyte ratio have also shown to be simple to use and extremely good markers of severity in pneumonia.[19,20] NLR integrates two types of immune responses to infection (neutrophilia and lymphopenia), making it a substantial prognostic marker in

https://doi.org/10.1016/j.arbres.2021.08.006

pneumonia.[19,21,22] Importantly, these markers are easily obtainable at hospital admission; clinicians should therefore implement them in clinical practice.

Recent studies have also explored the application of machine learning algorithms to support clinical decisions related to CAP.[23–25] It is the latest interesting approach in managing pneumonia. However, validations of the algorithms developed are necessary to implement such a tool in the future.

Continuing, due to the difficulty posed in determining microbial etiology, antibiotic therapy for pneumonia must be empirical.[4] Controversy concerning what empirical antibiotic therapy is the most adequate for pneumonia, especially in severe cases, very old and/or immunocompromised patients, is present, though. Similarly, there has yet to be an established consensus on the optimal duration of antibiotic therapy in cases of pneumonia. Compounding this is the added, continuous debate about what indications are adequate for corticosteroid use, especially in light of the recent impact of corticosteroids in patients with severe COVID-19.[26,27] Lastly, despite great efforts made by an expert panel to develop clinical guidelines, there are still gaps in the quality and quantity of studies on which the guidelines are based. The majority of studies are observational, and there are few randomized controlled trials (RCT). Also, most studies have focused on non-severe pneumonia and in immunocompetent individuals. As a result of such study characteristics, information regarding the very old population is limited and thereby places a cap on generalizations. Studies undertaken in the future will need to consider different antibiotic regimens, newer antibiotics and antibiotic therapy duration, especially in those patients who are critically ill, very old or immunocompromised. Furthermore, prospective studies will need to provide a better characterization of patients with pneumonia who could stand to benefit from corticosteroids as adjunctive therapy. New data of this nature would address existing disparities in these important issues on pneumonia.

Of note, we would like to reiterate that pneumonia is a preventable disease with well-known risk factors.[4,28–30] Effective vaccines such as *Haemophilus influenzae* type b, *pneumococcal* and influenza vaccine could reduce the burden of pneumonia on the most vulnerable populations globally. For example, pneumococcal conjugate vaccines (PCVs) have significantly reduced pneumococcal disease worldwide.[31] However, there are limitations in serotype coverage by PCV13 vaccine due to the evolution and emergence of new pneumococcal serotypes.[32] Developing new formulation of PCV vaccines—such as the 20-valent PCV (PCV20) that contains the capsular polysaccharide conjugates of serotypes present in the PCV13 plus 7 new serotypes (8, 10A, 11A, 12F, 15B, 22F, and 33F)[33] and the 15-valent PCV (PCV15) that contain scapsular polysaccharide conjugates of serotypes present in the PCV13 plus serotypes 22F and 33F[34]—are essential to reduce the burden of pneumococcal disease. However, while European vaccination programs are well-established for children and adults,[35] vaccination coverage remains suboptimal among the adult population. Low- and middle-income countries experience low vaccination coverage. According to the World Health Organization, approximately 19 million children aged < 1 year have not received basic vaccines, including the pneumococcal vaccination.[36] In the next, few years, routine vaccination programs for children and adults will require a boost in support and uptake worldwide.

Finally, it is vital to remark the importance of preventing aspiration pneumonia. This type of pneumonia remains poorly recognized, even though it has increased especially among very old, frail patients and is a cause of severe disease.[37] Studies focusing on preventive strategies for modifiable risk factors, such as oropharynx colonization, modifying gastric pH and dysphagia, are necessary to reduce their prevalence.

This all stated, we believe that governments must invest more in clinical research on pneumonia and strengthen investigation teams as they strive to pursue high-quality evidence related to different aspects of pneumonia. Although the COVID-19 pandemic has placed great pressure on health systems across the globe, governmental actions of such a magnitude would serve to create specific, national strategies to control pneumonia and improve vaccine uptake, risk factors, diagnosis and treatment of pneumonia. Only through developing concrete approaches and bettering the quantity and quality of scientific evidence on pneumonia will we be able to reduce the high burden of pneumonia and avoid deaths of the most vulnerable populations.

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