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Community-acquired Pneumonia Owing to Multidrug-Resistant Pathogens: A Step toward an Early Identification

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Community-acquired pneumonia (CAP) continues to be one of the leading causes of hospitalization and is associated with a high risk of morbidity and mortality, particularly in elderly patients with multiple comorbidities (1–3). Historically, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Legionella* spp. have accounted for the main causes of CAP in patients presenting to the emergency department (4). However, over the past decades, some organisms traditionally associated with the healthcare setting, such as *Pseudomonas aeruginosa*, extended-spectrum β-lactamase–producing *Enterobacterales*, and methicillin-resistant *Staphylococcus aureus* (PES pathogens), have emerged as causes of pneumonia in the community (5). Moreover, the diffusion of multidrug-resistant (MDR) bacteria in the community became an important public health threat (6): nowadays, carbapenem-resistant *Enterobacterales*, MDR *Pseudomonas aeruginosa*, and *Acinetobacter baumannii* are increasingly isolated in patients living at home or in long-term care facilities and represent a considerable challenge for clinicians because of the high mortality rates and limited available treatment options (7).

Since the delay in appropriate therapy may lead to worsened outcome, the identification of patients with CAP at high risk for resistant etiology is of outstanding clinical interest. The concept of healthcare-associated pneumonia (HCAP) was created to identify pneumonia in nonhospitalized patients who had significant experience with the healthcare system (8). However, this classification is not without limitations and may be overly sensitive, leading to inappropriately broad antibiotic use. On one hand, the incidence of MDR organisms among patients who meet criteria for HCAP ranges from 10% to 30% (5). On the other hand, about 30% of patients with pneumonia caused by MDR organisms are classified as CAP and not as HCAP (5). It appears clear that the HCAP definition does not completely mirror the probability of resistant etiology in patients with pneumonia living in the community.

To assist clinicians to select patients who need antibiotics active against nosocomial organisms, some tools have been proposed to replace the HCAP label (5, 9–11). The application in clinical practice of these risk scores could help in developing strategies to balance the need to treat infections appropriately while avoiding the overuse of broad-spectrum antibiotics. Ideally, a risk score that identifies patients with CAP who need antibiotic coverage against nosocomial pathogens should be easy to be applied in the emergency department, rapidly calculable from all physicians, and replicable and generalizable to settings with incidence of different MDR organisms. None of the currently available scores have all these features simultaneously. The ARUC score needs imaging and blood gas analysis to detect bilateral pulmonary infiltration or pleural effusion and partial pressure arterial oxygen/fraction of inspired oxygen ratio <200, respectively (5). The Aliberti score requires an in-depth medical history and also takes into account patients from nursing homes or those who receive immunosuppressive therapy (9). The tool by Shorr and colleagues was derived and validated more than 10 years ago and includes the intensive care unit (ICU) admission, which may be considered an outcome rather than a surrogate predictor of MDR etiology (10). Finally, the drug resistance in pneumonia (DRIP) score considers anamnestic risk factors but not severity of pneumonia (11).

In this issue of *AnnalsATS*, the study by Ceccato and colleagues (pp. 257–265) tried to validate a score for predicting PES microorganisms in patients with CAP (12). This score has some differences compared with the previous ones. First, it has been validated in two different cohorts of patients (Valencia and Mataro) with different disease severity. Compared with the Valencia cohort (the non-ICU cohort), the Mataro group (ICU cohort) had a higher proportion of severe CAP, with 53% of patients presenting with septic shock and 62% needing invasive mechanical ventilation. Nevertheless, the PES score retained a negative predictive value above 95% in both cohorts. This may indicate a good applicability of PES score in patients with CAP hospitalized in medical wards or in the ICU. Second, the PES score aimed to identify CAP by three specific pathogens (PES), narrowing the spectrum of causative strains to the most

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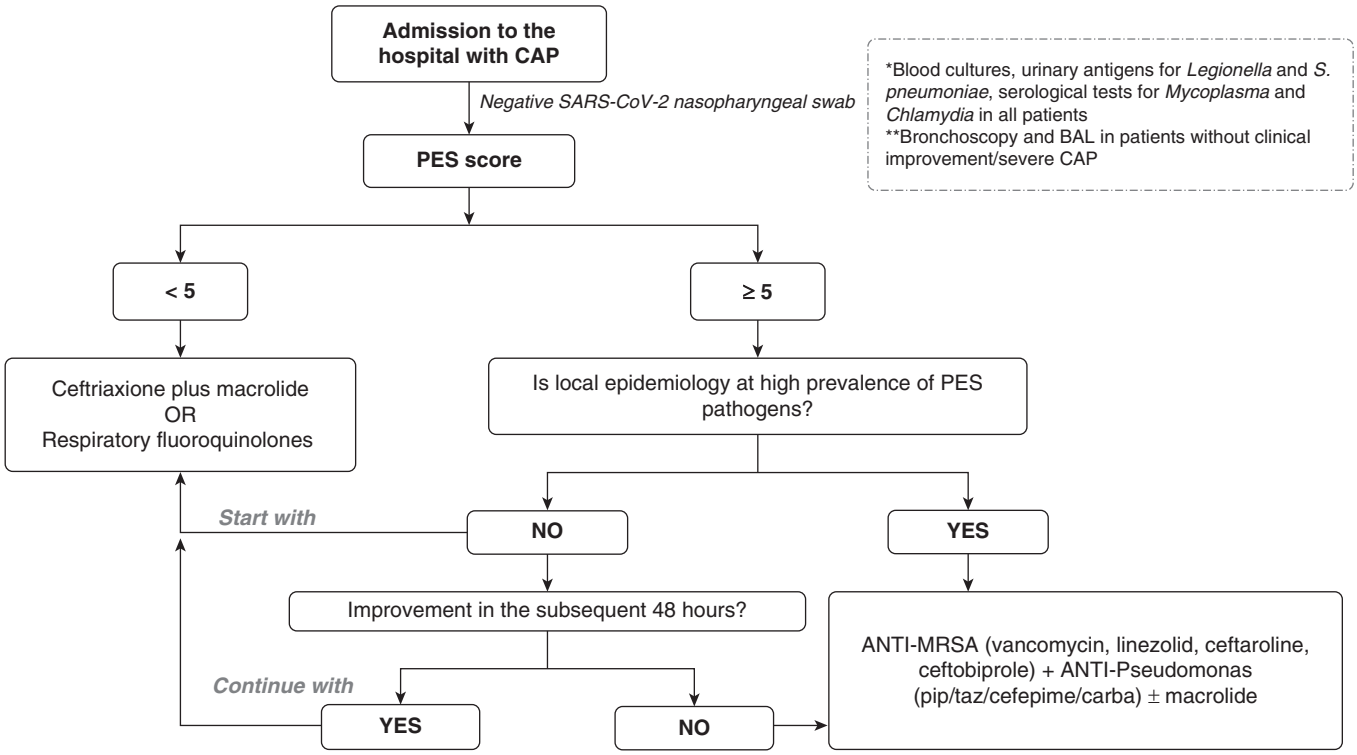

Figure 1. Proposed algorithm for the therapeutic decision in patients with community-acquired pneumonia admitted to the emergency department. BAL = bronchoalveolar lavage; CAP = community-acquired pneumonia; MRSA = methicillin-resistant *Staphylococcus aureus*; PES = *Pseudomonas aeruginosa*; SARS-CoV-2 = severe acute respiratory syndrome coronavirus 2.

common resistant organisms in the community (12). Third, the PES score combines three types of information: the patient's demographic data (age and sex), medical history/comorbidities (previous antibiotic use, chronic renal failure, or chronic respiratory disorders), and severity of illness at emergency department admission (consciousness impairment or lack of fever), looking at the patients in their entirety.

PES score may be easily applied in the clinical practice, and its high negative predictive value (98%) allows clinicians to rule out patients not needing antibiotic coverage against PES with a good confidence.

However, clinical judgment and local epidemiology should not be underestimated. Combining the PES score, epidemiological data, and clinical evaluation, we proposed an algorithm to guide early antibiotic therapy in patients with CAP (Figure 1). Considering its high negative predictive value, when PES on admission is negative (<5), clinicians can start a standard therapy for the treatment of CAP (ceftriaxone plus macrolide or respiratory fluoroquinolones). Conversely, if PES score is 5 or more, local epidemiology should be considered. A high local prevalence of resistant organisms in the community may guide clinicians to start a broad spectrum antibiotic therapy early, also covering PES organisms; in an area with low prevalence of community PES, standard therapy for CAP may be started and the patient reevaluated after 48 hours to decide to continue (if clinical improvement) or escalate (in the absence of clinical amelioration) antibiotic therapy. It should always be considered that efforts to identify the causative pathogen are crucial, especially in patients without clinical response or those affected by severe pneumonia. An important step in the proposed algorithm is the evaluation of the local epidemiology: data from European Centre of Disease Control and Prevention showed that Italy, Spain, and Balkan countries are those at highest prevalence of third-generation cephalosporin-resistant *Escherichia coli* and fluoroquinolones-resistant *Pseudomonas aeruginosa* (13). Calculating the negative predictive value of the PES score in countries with high prevalence of antimicrobial resistance in the community might be interesting (14).

Unfortunately, the score by Ceccato and colleagues does not take into account the probability to be infected by pathogens other than PES, such as carbapenem-resistant *Enterobacterales*, *A. baumanni*, or other MDR nonfermenting rods. Although less common, these organisms may cause CAP in endemic settings. During the recent outbreak of New Delhi Metallo-β-Lactamase (NDM)–producing *Enterobacterales* in Italy, a significant proportion of patients with infections caused by NDM-producing strains came from the community, so active surveillance procedures in the emergency department became crucial to identify infected patients early (15). Among the two cohorts in which the PES score was validated, the MDR rates were very low (3% for *P. aeruginosa* in the Valencia cohort and zero in the Mataro cohort). Thus, PES score does not help to identify such patients. In these specific settings, other instruments are needed to support the therapeutic decision process.

Future approaches may be important to overlap limitations of risk scoring: a comprehensive molecular testing approach may double pathogen detection in patients with CAP, providing information about individual bacterial loads and guiding treatment decisions with significantly more information (16). The use of artificial intelligence (e.g., machine learning) represents an appealing instrument to support clinical decision-making processes in patients with CAP. Future studies are needed to assess the value of these approaches. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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Azithromycin and Tobramycin Therapy in Cystic Fibrosis Pulmonary Exacerbations: Less Is More?

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Pseudomonas aeruginosa (*Pa*) is a principal pathogen in the lower airways of individuals with cystic fibrosis (CF), and chronic infection is associated with negative clinical outcomes, including decreased lung function (percentage predicted forced expiratory volume in 1 second [ppFEV$_1$]), risk of pulmonary exacerbations (PEx), and reduced survival (1–4). For decades, tobramycin has been used in the treatment of *Pa* for eradication, chronic suppression, and treatment of acute PEx. Chronic azithromycin (AZM) therapy, though not directly antipseudomonal, has become increasingly used (estimated 64% of persons aged 6 years and older) over the last decade, aiming to reduce the frequency of PEx in patients with CF bronchiectasis with or without chronic *Pa* infection (5, 6). Patients are often treated with multiple antipseudomonal therapies, including AZM and tobramycin, in combination to optimize clinical outcomes in both the acute and chronic settings. As medications tend to be additive over time in a person's disease course, the potentially antagonistic drug interactions are often overlooked. Encouragingly, recent studies have endeavored to evaluate just this and have identified antagonistic *in vivo* (7) and *in vitro* (8) interactions between commonly concurrently prescribed AZM and tobramycin in *Pa* infection.

In this issue of *AnnalsATS*, Cogen and colleagues (pp. 266–272) report the first and largest study addressing the relationship between concomitant chronic AZM and parenteral tobramycin use during acute PEx in patients with CF on clinical outcomes (9). They conducted a retrospective cohort study using the CF Foundation Patient Registry–Pediatric Health Information System (10) linked dataset and analyzed 2,294 children and adolescents with CF aged 6–21 years with 5,022 PEx across 45 U.S. hospitals between 2006 and 2016. An

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