Too Much or Too Little Empiric Treatment for *Pseudomonas aeruginosa* in Community-acquired Pneumonia?

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Pseudomonas aeruginosa (PA) is a recognized cause of community-acquired pneumonia (CAP) in nonimmunosuppressed patients, but its exact incidence is not known, nor how often this pathogen should be targeted by empiric therapy. Prior studies of heterogenous populations have reported variable rates, but three single-center and multicenter observational studies using similar methods have described a 4–5% incidence rate in nonimmunocompromised patients with CAP (1–4). In 30–50% of PA cases, the organisms were resistant to one or more antibiotics, and these patients would not be adequately treated by standard CAP therapy (2–4). In addition, PA CAP has been associated with a high 30-day mortality, making it imperative to identify potentially infected individuals.

In CAP guidelines, the necessity for empiric PA coverage has changed over time, with fewer patients qualifying in more recent guidelines compared with older recommendations. In the most recent American Thoracic Society and the Infectious Diseases Society of America (ATS/IDSA) guidelines, healthcare-associated pneumonia was excluded as a form of CAP, and recommended empiric therapy was with a non–anti-Pseudomonal β-lactam, plus or minus a macrolide or respiratory fluoroquinolone (levofloxacin or moxifloxacin) (5). This treatment, however, does not cover PA, and the guidelines recommend empiric anti-Pseudomonal therapy only for patients with nonsevere illness and prior respiratory tract cultures showing PA or those with severe CAP who have either prior PA colonization or the presence of locally validated risk factors for PA (which generally are not well defined or specific) (5). In both instances, discontinuation of this coverage was recommended if the organism was not present in the current respiratory culture. The overall goal is to provide PA coverage for those who need it while avoiding overuse of broad-spectrum empiric therapy, which can result in an increased risk of future development of resistance.

In this issue of *AnnalsATS*, Sando and colleagues (pp. 1475–1481) have reported a new approach to this problem (6). They looked at 2,701 Japanese patients with CAP and found that 0.9% (n = 25) had "definitive" PA pneumonia, whereas 4.9% had "indeterminate" PA CAP, with each group having different clinical characteristics. The sum of both groups (indeterminate + definitive) is similar to the frequency of PA CAP mentioned above. Definitive PA was defined as a positive blood culture for PA, with a good-quality sputum sample containing gram-negative rods, likely corresponding with PA, and predominant growth in a culture of $\geq 1 \times 10^6$ CFU/ml or a score of 3+ in a semiquantitative evaluation. Indeterminate PA CAP was defined when PA was isolated from sputum without meeting definitive PA criteria. When the authors compared definitive and indeterminate PA with non-PA, they found that those with definitive PA were more likely to have a history of tuberculosis and chronic obstructive pulmonary disease (COPD)/bronchiectasis, whereas patients with indeterminate PA presented with more comorbidities than those with non-PA CAP (nursing home, oral steroids, neuromuscular disease, low body mass index, prior hospitalization, prior pneumonia, vital sign abnormalities, hypoalbuminemia, or requiring help for daily living activities). Although the study suggests that the prevalence of PA CAP is perhaps lower than imagined, it is unclear if cases of indeterminate PA represent colonization that does not warrant anti-Pseudomonal treatment. Although the authors suggest that many indeterminate patients did not need anti-Pseudomonal therapy, this remains uncertain. In fact, if the patient was known to be colonized, the new ATS/IDSA guidelines recommend anti-Pseudomonal therapy without deescalation if current cultures were positive (5). This is especially the case for those with severe illness, a factor not considered by Sando and colleagues.

In real clinical settings, many hospitalized patients with CAP receive one or two anti-Pseudomonal drugs. In the study above, 88% with definitive PA infection got one or two anti- Pseudomonal drugs, whereas 60% with indeterminate PA infection also got this therapy, along with 25% without PA infection. Although we are uncertain whether therapy of the indeterminate group was necessary, we do think that coverage of those without PA infection is an opportunity for deescalation and antimicrobial stewardship. Overall, patients without PA received anti-Pseudomonal therapy for a median of 6 days, and only 21% had deescalation. Although not explained in the manuscript, possible reasons for overuse of anti-

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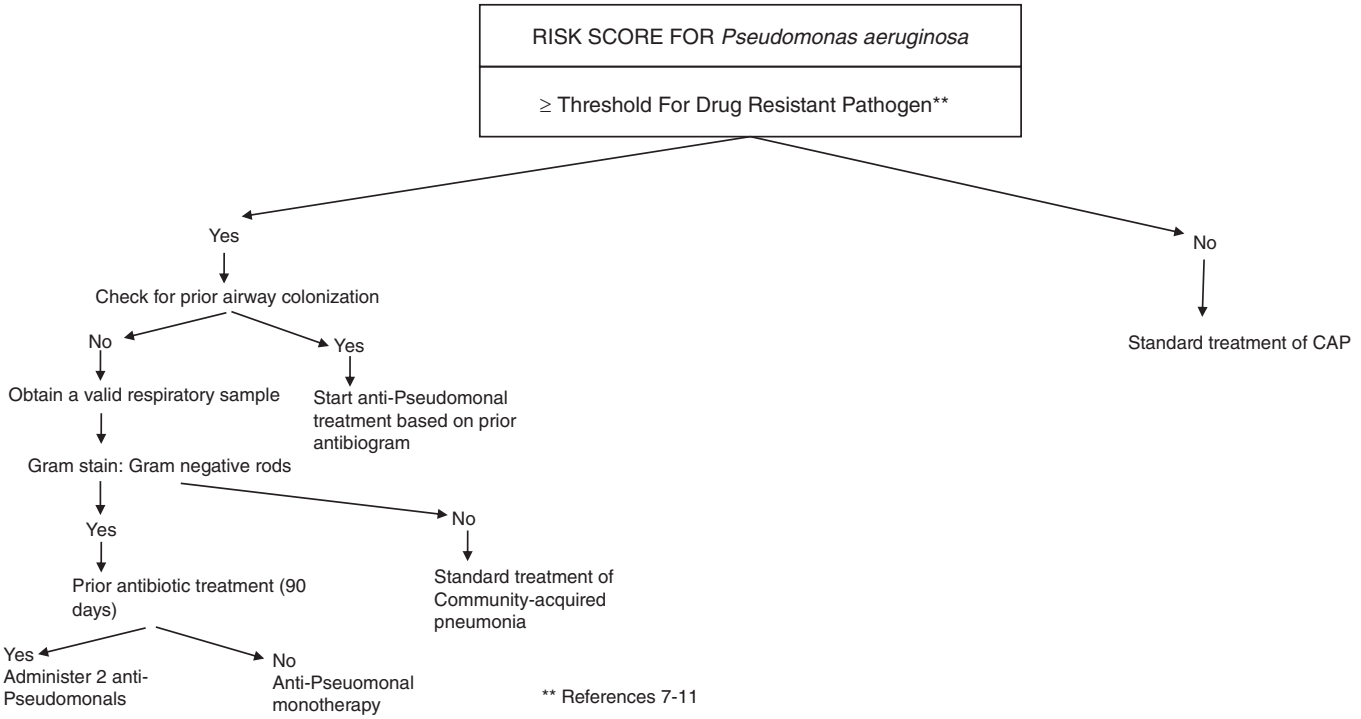

Figure 1. An algorithm to guide when to use empiric anti-Pseudomonal therapy for community-acquired pneumonia. This algorithm combines data from scoring systems (7–11) along with Gram staining of a lower respiratory tract sample and historical data about prior antibiotic use and prior respiratory tract colonization by *Pseudomonas aeruginosa*. CAP = community-acquired pneumonia.

Pseudomonal therapy include continued use in those with healthcare-associated pneumonia, not following established guidelines, and lack of awareness of clinical risk factors for PA.

One way to also promote more responsible use of anti-Pseudomonal therapy, in addition to deescalation, is to use scoring systems to identify high-risk patients as soon as possible, particularly in the emergency department, when severe illness is present. Several approaches have been developed to address risk factors (7–10), including patient populations with some type of immunosuppression, such as human immunodeficiency virus (7). However, not all such scores are validated. The PES score published by Prina and colleagues in 2015 (11) came from a single-center study of a large cohort of nonimmunosuppressed patients with CAP. PES is an acronym for PA, extended-spectrum β-lactamase *Enterobacteriaceae* and methicillin-resistant *Staphylococcus aureus*—all microorganisms not covered by standard recommended treatment. This score includes age (0–2 points), male sex (1 point), previous antibiotic use (2 points), COPD or bronchiectasis (2 points), chronic renal disease (3 points), and, in the emergency department, impaired consciousness (2 points) and fever (−1 point). A score of 5 points or more was highly predictive of a PES organism. This score was validated recently (in two CAP cohorts in Spain, including one admitted to the intensive care unit) (12). The AUC for the overall population was 0.78, and the negative predictive value was 97%, with a low predictive value of 13%. Because of its high negative predictive value, the PES score could be used initially to rule out patients who need broad-spectrum empiric antibiotic treatment.

Although the PES score cannot discriminate between *Pseudomonas* and extended-spectrum β-lactamase *Enterobacteriaceae* or methicillin-resistant *S. aureus*, it is easily calculable at the bedside. Although it may not identify all at-risk patients, those with a high score should have a valid respiratory sample collected for Gram staining and culture (which is not always done but is recommended with specific criteria by Sando and colleagues) (6). If Gram staining shows gram-negative rods (one criteria of definitive PA CAP), the finding can reinforce the clinicians' decision to cover PA (13).

Beyond this, prior respiratory colonization is not only a PA risk factor, and those with COPD and bronchiectasis might have sputum cultures collected before admission, but the antibiotic susceptibilities can guide the choice of anti-Pseudomonal treatment. If the patient has received prior antibiotics in the past 90 days, resistance is more likely, and we recommend empirically starting two anti-Pseudomonal antibiotics and deescalating when an antibiogram becomes available (Figure 1)

We are concerned that overtreatment of PA in CAP remains extremely frequent, even though the prevalence of this organism is low. At the same time, we need to use appropriate empiric therapy in high-risk patients. Validated scoring systems may help us to address this conundrum and are

generally supported by the latest ATS/IDSA recommendations. In highly suspected cases of PA in CAP, the algorithm in Figure 1 guides empiric anti-Pseudomonal therapy, but this approach also requires rigorous use of deescalation whenever possible as part of responsible stewardship. ■

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

References

1 Torres A, Cilloniz C, Niederman MS, Menéndez R, Chalmers JD, Wunderink RG, *et al.* Pneumonia. *Nat Rev Dis Primers* 2021;7:25.
2 Cillóniz C, Gabarrús A, Ferrer M, Puig de la Bellacasa J, Rinaudo M, Mensa J, *et al.* Community-acquired pneumonia due to multidrug- and non-multidrug-resistant Pseudomonas aeruginosa. *Chest* 2016;150: 415–425.
3 Sibila O, Laserna E, Maselli DJ, Fernandez JF, Mortensen EM, Anzueto A, *et al.* Risk factors and antibiotic therapy in P. aeruginosa community-acquired pneumonia. *Respirology* 2015;20:660–666.
4 Restrepo MI, Babu BL, Reyes LF, Chalmers JD, Soni NJ, Sibila O, *et al.*; GLIMP. Burden and risk factors for *Pseudomonas aeruginosa* community-acquired pneumonia: a multinational point prevalence study of hospitalised patients. *Eur Respir J* 2018;52:1701190.
5 Metlay JP, Waterer GW, Long AC, Anzueto A, Brozek J, Crothers K, *et al.* Diagnosis and treatment of adults with community-acquired pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America. *Am J Respir Crit Care Med* 2019;200:e45–e67.
6 Sando E, Suzuki M, Ishida M, Yaegashi M, Aoshima M, Ariyoshi K, *et al.* Definitive and indeterminate *Pseudomonas aeruginosa* infection in adults with community-acquired pneumonia: a prospective observational study. *Ann Am Thorac Soc* 2021;18:1475–1481.
7 Aliberti S, Di Pasquale M, Zanaboni AM, Cosentini R, Brambilla AM, Seghezzi S, *et al.* Stratifying risk factors for multidrug-resistant pathogens in hospitalized patients coming from the community with pneumonia. *Clin Infect Dis* 2012;54:470–478.
8 Shorr AF, Zilberberg MD, Reichley R, Kan J, Hoban A, Hoffman J, *et al.* Validation of a clinical score for assessing the risk of resistant pathogens in patients with pneumonia presenting to the emergency department. *Clin Infect Dis* 2012;54:193–198.
9 Webb BJ, Dascomb K, Stenehjem E, Vikram HR, Agrwal N, Sakata K, *et al.* Derivation and multicenter validation of the drug resistance in pneumonia clinical prediction score. *Antimicrob Agents Chemother* 2016;60:2652–2663.
10 Falcone M, Russo A, Giannella M, Cangemi R, Scarpellini MG, Bertazzoni G, *et al.* Individualizing risk of multidrug-resistant pathogens in community-onset pneumonia. *PLoS One* 2015;10:e0119528.
11 Prina E, Ranzani OT, Polverino E, Cillóniz C, Ferrer M, Fernandez L, *et al.* Risk factors associated with potentially antibiotic-resistant pathogens in community-acquired pneumonia. *Ann Am Thorac Soc* 2015;12: 153–160.
12 Ceccato A, Mendez R, Ewig S, de la Torre MC, Cilloniz C, Gabarrus A, *et al.* Validation of a prediction score for drug-resistant microorganisms in community-acquired pneumonia. *Ann Am Thorac Soc* 2021; 18:257–265.
13 Taniguchi T, Tsuha S, Shiiki S, Narita M. Gram-stain-based antimicrobial selection reduces cost and overuse compared with Japanese guidelines. *BMC Infect Dis* 2015;15:458.

The Societies' Responsibility for Wellness: Healing for the Healer

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Critical care practitioners have a moderate degree of resilience despite the stress-charged environment in which we work (1–3). We have chosen to work in this field. But constant traumatic events, particularly the experiences of the pandemic over the past 18 months, have stretched our limits (4–6). We work in an environment where moral distress and compassion fatigue are factors that lead to high rates of burnout among healthcare professionals (7, 8). Healthcare professionals who care for the sickest of the sick are constantly exposed to traumatic events (9). How can strategies that are used to support survivors of trauma (10) also be applied to those who work in sustained high stress environments? What are the wellness strategies that can be used to support healthcare workers?

Wellness is both a personal- and systems-level issue (11). Maintaining individual physical and mental health is usually taught at an early age or developed as part of a personal health strategy. The societal responsibility for wellness is a developing trend for healthcare professionals. In this issue of *AnnalsATS*, Rinne and colleagues (pp. 1482–1489) present their mixed methods study of 17 U.S. professional societies that support critical care practitioners (12). The investigators began with a survey of the burnout prevention and wellness initiatives as well as a search of the society's website for additional information. This was followed by interviews with the society representative best in a position to speak on the initiatives and how they related to both the directives provided by the Critical Care Societies Collaborative (13) and the