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Commentary

Finding the balance between overtreatment versus undertreatment for hospital-acquired pneumonia

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Hospital-acquired pneumonia (HAP) is the most common and deadly healthcare-associated infection, and antibiotic prescribing for possible HAP is one of the most common drivers of broad-spectrum antibiotic use in hospitals.[1,2] A point-prevalence study conducted by the US Centers for Disease Control and Prevention estimated that HAP affects ~1 in 100 admissions.[1] Crude mortality rates for HAP range from 15% to 30%.[3] Far more than 1% of hospitalized patients receive antibiotics for possible pneumonia, however, because of the inherent difficulty accurately diagnosing pneumonia.[4] The signs and symptoms of pneumonia are neither sensitive nor specific and a host of conditions common in hospitalized patients have overlapping clinical signs including heart failure, atelectasis, mucous plugging, obstructive lung disease, thromboembolic disease, hypersensitivity reactions, lung contusions, pulmonary hemorrhage, and more.[5] The issue is further complicated by the challenge of differentiating colonization from infection. Positive sputum cultures do not always reflect what is (or is not) in the lungs, particularly in intubated patients.

The dilemma for clinicians and antibiotic stewards, however, is that notwithstanding the difficulty diagnosing HAP, there is a sense that is imperative to start broad-spectrum antibiotics in patients with possible HAP as soon as possible. This sense of urgency is borne of the literature showing associations between delays in starting active antibiotics and higher mortality rates.[6] This concern has been amplified by care improvement initiatives like the Surviving Sepsis Campaign and the Centers for Medicare and Medicaid Services' sepsis care mandate that set aggressive time-to-treatment goals for patients with possible sepsis. The net products of diagnostic uncertainty, fear of causing harm through delay, and regulatory proclamations, however, are a high rate of overtreatment and overly broad treatment. At least one-third of patients started on antibiotics for possible HAP have other conditions and the majority do not have drug-resistant pathogens.[4,5,7–9]

A new study by Zilberberg et al[10] provides helpful new data on the pathogens and antibiotic susceptibilities associated with HAP to inform the calculus clinicians face in trying to balance the risk of undertreatment against the risk of overtreatment. The investigators queried electronic data from 253 US hospitals and identified 17,819 patients hospitalized between 2013 and 2019 with possible HAP. Cases were detected using a combination of discharge diagnosis codes, positive blood or respiratory cultures on hospital day ≥3, and treatment with ≥3 days of antibiotics starting on the day the blood or respiratory culture turned positive. Approximately half the patients had ventilator-associated pneumonia and half had nonventilator hospital-acquired pneumonia (NV-HAP). Of the patients with NV-HAP, about half required mechanical ventilation and half did not. The pathogens associated with VAP, NV-HAP requiring mechanical ventilation, and NV-HAP not requiring mechanical ventilation were relatively similar: *Staphylococcus aureus* accounted for about 40%, *Pseudomonas aeruginosa* accounted for 17%–19%, *Klebsiella pneumoniae* accounted for 12%–13%, and *Escherichia coli* accounted for 9%–13%. Antibiotic resistance rates were also fairly similar across all 3 HAP types: about 40% of *Staphylococcus aureus* isolates were methicillin resistnat, 13%–15% of gram negative isolates were resistant to third-generation cephalosporins, 7%–9% were resistant to carbapenems, and 15%–16% were resistant to anti-pseudomonal β-lactams.

The investigators went on to characterize the frequency of inappropriate empiric therapy and its potential impact on patient outcomes. Inappropriate empiric regimens were prescribed for 7% of patients with VAP, 6% of patients with NV-HAP requiring mechanical ventilation, and 9% of NV-HAP who did not require mechanical ventilation. Inappropriate empiric therapy was associated with longer lengths of stay (1.8 extra days for VAP, 2.3 extra days for NV-HAP requiring mechanical ventilation, 8.7 extra days for NV-HAP not requiring mechanical ventilation) and higher hospital costs but not with increased mortality or 30-day readmissions. These researchers concluded based on this analysis that all patients with HAP require empiric regimens targeting extended-spectrum β-lactamase producers and carbapenem-resistant organisms.

As with any problem, however, there is another perspective. Antibiotic resistance rates of 7%–16% can also be read as antibiotic susceptibility rates of 84%–93%. Although there is a general perception that antibiotic resistance is rampant in hospital-acquired infections, in practice, in many locations, antibiotic-resistant organisms account for a minority of infections.[8] A general directive to include carbapenems in all empiric regimens for HAP will mean treating at least 85% of patients with a broader regimen than they require. Requiring clinicians to use our precious few agents active against carbapenem-resistant organisms for every possible HAP even more so. Indeed, the potential for overtreatment may be even higher: the authors' analysis was limited to patients with positive

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cultures. This likely exaggerates the frequency of antibiotic resistance by focusing just on patients able to produce sputum or who get intubated, a subgroup in whom the diagnosis of pneumonia is more likely and more severe. It also does not take into account the high rate of pneumonia overdiagnosis and our increasing recognition that a substantial fraction of HAP is viral rather than bacterial.[11–13] These patients are exposed to all the potential harms of antibacterial treatment and none of the benefits.

The high risk of overtreatment is not a trivial issue; more and more data have emerged indicating that overtreatment can be as harmful as undertreatment. One study, for example, found that unnecessarily broad antibiotic regimens for patients with sepsis were associated with increased risk for hospital death, acute kidney injury, and *Clostridioides difficile* infection.[14] Another analysis found that empirical anti-MRSA therapy for pneumonia was associated with increased risk of death, kidney injury, *C. difficile* infection, vancomycin-resistant *Enterococcus* infections, and secondary gram-negative infections.[15]

Nonetheless, we still have to contend with the counterbalancing risk of undertreatment for the subset of patients who do have resistant organisms and who may be at risk for worse outcomes if appropriate treatment is delayed. A number of potential strategies are emerging to help clinicians navigate the fine line between overtreatment versus undertreatment. One of the most promising avenues is rapid diagnostic tools, including viral multiplex testing, which can identify both pathogens and antibiotic susceptibility patterns. These technologies are still largely experimental, none have yet been shown to clearly improve patient outcomes in rigorous randomized trials, but they clearly have the potential to provide clinicians with actionable information in actionable time frames that could facilitate choosing narrower spectrum treatments.

Rapid microbiological diagnostics will not, however, be a panacea. We will still have to contend with (1) the diagnostic uncertainty associated with suspected HAP leading to high rates of overdiagnosis, (2) our failure to get respiratory cultures to inform diagnostics in more than two-thirds of patients, and (3) physicians' hesitancy to trust that rapid diagnostic platforms are sufficiently sensitive to allow them to safely withhold broad-spectrum agents. It is critical, therefore, to also guide clinicians to apply more nuance to the questions of when and what antibiotics to deploy when they suspect HAP.

Not every patient with possible HAP requires immediate antibiotics.[16,17] In a subset of patients with less severe disease, short delays to gather more diagnostic data to help rule in or out bacterial pneumonia have not been associated with harm.[18–20] Indeed, the 2021 version of the Surviving Sepsis Campaign guidelines explicitly guides clinicians to balance patients' severity of illness against their likelihood of infection to determine antibiotic urgency.[21] The new guidelines state that antibiotics should only be given immediately to patients with possible septic shock or clear evidence of infection. For those without septic shock, clinicians should seek more data before starting antibiotics. This could include additional diagnostics (eg, cultures, viral assays, cross-sectional imaging, etc) and/or therapeutic challenges for other potential causes of pulmonary syndromes as appropriate (eg, diuresis, pulmonary toilet, bronchodilators, anticoagulants, recruitment trials, etc). If, after these measures, infection still seems likely, then patients should be treated. If not, clinicians can continue to observe alone. Notably, in the cohort analyzed by Zilberberg et al,[22] septic shock was only present in 19% of patients with VAP, 32% of patients with NV-HAP requiring mechanical ventilation, and 12% of patients with NV-HAP without mechanical ventilation. These findings suggest that, with close monitoring, it may be safe to hold antibiotics in most patients with possible HAP while gathering more data to confirm the diagnosis and establish the causative pathogen.

More broadly, the best way to minimize overtreatment of HAP is to prevent it in the first place. We still have large opportunities to improve HAP prevention programs.[23] Most hospitals only have initiatives directed at preventing VAP despite the fact that most HAP occurs in nonventilated patients. Exemplar prevention programs are beginning to emerge that will hopefully catalyze more widespread efforts to prevent this most common and deadly of hospital-acquired infections.[24]

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