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EDITORIAL

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"Does this patient have…" "Is this patient at risk for infection with multidrug resistant bacteria?"

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A 67-year-old woman with insulin-dependent diabetes and end-stage renal disease receiving outpatient hemodialysis has been hospitalized twice over the past 10 weeks with acute pneumonia and respiratory failure. Given her prior hospitalizations with antibiotic exposure, this patient would appear to be at increased risk for infection with potentially antibiotic-resistant bacteria. Antibiotic resistance has emerged as one of the most important determinants of outcome in patients with serious infections along with the virulence of the underlying pathogen. Antimicrobial resistance is a growing challenge in the care of critically ill patients. Escalating rates of antibiotic resistance add substantially to the morbidity, mortality, and costs of infections in the ICU setting [1]. Both Gram-positive organisms, such as methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE), and Gram-negative bacteria, including *Pseudomonas aeruginosa*, *Acinetobacter* species, and *Klebsiella pneumoniae* carbapenemase (KPC)-producing bacteria have contributed to the escalating rates of multidrug resistant (MDR) bacteria accounting for infections in the ICU.

The mechanism for poor outcomes with antibiotic-resistant organisms is not entirely clear. In general, these bacteria are not believed to be inherently more virulent than similar susceptible species. Resistance and its rapid evolution, however, make efforts to insure initial appropriate antibiotic therapy (IAAT) more difficult, and IAAT is a key determinant of outcome in severe infection [2]. IAAT has consistently been shown to reduce mortality rates in severe sepsis and septic shock, and the Surviving Sepsis Guidelines strongly support initiatives to guarantee that patients receive timely antibiotic treatment [3]. Yet, not all serious infections are due to MDR organisms, so clinicians must have a strategy for determining which patients should be treated with broad-spectrum antibiotics. Minimizing the unnecessary use of antibiotics is a fundamental principle of antimicrobial stewardship that should be followed by all intensivists [4]. The challenge is how to best optimize antibiotic decision-making in the ICU in order to reduce resistance emergence.

Traditionally, the goal for clinicians has been to understand patient characteristics that increase the risk for infection due to MDR pathogens above a certain threshold where broader empirical antibiotics would be needed. More recently, in the face of rising rates of resistance, the focus has shifted towards excluding patients at minimal risk for MDR bacteria, thus limiting unnecessary broad-spectrum agents and helping to contain costs and reduce future antibiotic resistance. The identification of MDR risk factors has best been explored for pneumonia. The importance of pneumonia in this context is highlighted by the use of the term "healthcare-associated pneumonia" (HCAP) which is aimed at identifying patients at higher risk for infection with antibiotic-resistant bacteria. However, the HCAP classification has come under fire as it may promote unnecessary use of broad-spectrum

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antibiotics, especially in clinical situations or regions without high risk for MDR bacteria [5]. This emphasizes a key principle of antimicrobial stewardship, namely clinicians should have a good understanding of the prevalence of MDR bacteria in their countries, cities, and the hospitals where they practice.

Another criticism of the HCAP definition was that it indiscriminately attributed the same weight to all criteria across all MDR pathogens [6]. Several other risk factor models have been developed as outlined in Table 1 [7–12]. These algorithms were locally developed by investigators, often with the assistance of outside experts, with the primary goal of improving upon the identification of patients with pneumonia attributed to antibiotic-resistant bacteria. Many of the risk factors employed in these models are surrogate variables for prior exposure to antibiotics. Indeed, our patient possessed several of these risk factors (prior antibiotic therapy, hemodialysis, prior hospitalization), placing her at increased risk for infection with MDR bacteria. Studies attempting to validate the

Table 1 Prediction criteria for pneumonia attributed to antibiotic-resistant bacteria

Prediction algorithm	Risk factors/prediction variables[a]	References
HCAP criteria	Hospitalized in the previous 90 days Nursing home resident Home infusion therapy Chronic dialysis Home wound care Family member with resistant bacteria	[6]
St. Louis, Missouri criteria	Hospitalized in the previous 90 days Nursing home resident Chronic dialysis ICU admission	[17]
Milan, Italy criteria	Comorbid conditions (cerebrovascular disease, diabetes, COPD) Antibiotics in prior 90 days Immunosuppression Home wound care Home infusion therapy Nursing home resident Hospitalized in prior 90 days Chronic renal failure	[8]
Joint Japanese–U.S. criteria	ICU admission Immunosuppression Hospitalized in prior 90 days Antibiotics in prior 6 months Poor functional status	[9]
Nagoya, Japan criteria	Hospitalized in prior 90 days Immunosuppression Antibiotics in prior 90 days Gastric acid suppression medication Tube feeding Nonambulatory status	[10]
Rome, Italy criteria	One risk factor for HCAP Bilateral infiltrates Pleural effusion paO_2/FiO_2 ratio <300	[11]
Spanish criteria HCAP	Hospitalization in previous 90 days Residence in a nursing home or extended care facility Home infusion of antibiotics Chronic hemodialysis Home wound care Family member colonized with MDR isolate	[12]
Spanish criteria ICP	HIV Organ transplant Chemotherapy, corticosteroids, other immunosuppressive therapy for at least 4 weeks prior to the diagnosis of pneumonia	[12]

HCAP healthcare-associated pneumonia, *COPD* chronic obstructive pulmonary disease, *ICU* intensive care unit, *MDR* multidrug resistant, *ICP* immunocompromised patient, *HIV* human immunodeficiency virus

[a] It is important to note that these risk factors should be assessed in the context of the local prevalence of MDR bacteria and are not necessarily specific markers for individual bacterial species

algorithms in Table 1 have demonstrated limited accuracy in the precision of these models when applied to an independent population, indicating again that local ecology and case mix drive the rates of MDR infection in differing regions and countries [5, 13, 14]. Similarly, specific HCAP risk factors and the presence of multiple HCAP risk factors have been linked to increased risk of pneumonia attributed to *S.aureus* and *P. aeruginosa*, respectively [15]. However, the clinical utility of these specific risk factor profiles for improving the prescription of antibiotics to patients with pneumonia has not been demonstrated.

Most risk factors are not microbe-specific: nursing home residence, prior antibiotic use, and critical illness have all been associated with multiple pathogens like *P. aeruginosa*, MRSA, VRE, etc. It is also not the mere presence of a single factor but the interaction between multiple risk factors that quantify the risk for antibiotic resistance. In general, patients admitted to the ICU, especially in tertiary care centers, are more likely to suffer from infections caused by MDR bacteria. However, it was thought that all nursing home residents were very likely to acquire MDR pathogens, but it is now understood that age, functional status and frequent hospital admissions associated with antibiotic treatment, and not solely the place of residence, predispose patients to resistant microbes. Previous antibiotic use appears to be the most important risk factor for MDR infection and creates an intricate pattern of resistance, not only by selecting resistant or hypermutant clones but also by inducing unexpected defense mechanisms against different classes of antimicrobials in various species of microbes. To further complicate the emergence of resistance, bacteria interact and promote each other constantly when colonizing and invading the human host (e.g., *Pseudomonas* promotes *S. aureus* colonization in cystic fibrosis).

Given the non-specificity of any single risk factor and the usual need for different classes of antibiotics, studies have tried to separate risk factors for MRSA from *Pseudomonas* pneumonias. With the emergence of new broad spectrum antibiotics, this separation may become unnecessary. While *Pseudomonas* infections are more likely to develop in patients with structurally damaged lungs, including chronic obstructive pulmonary disease (especially in the setting of prior antibiotic exposure), cerebrovascular disease and during the second episode of ventilator-associated pneumonia [16], MRSA pneumonia seems to preferentially affect elderly nursing home residents with previous hospitalizations and patients having received courses of antibiotics or tube feeds [10]. Moreover, it is important to recognize that, even in countries with low rates of MDR pneumonia, the presence of immunosuppression significantly increases the likelihood of infection with MDR Gram-negative bacteria and MRSA [12].

At the present time, the most logical approach for dealing with the conundrum of how and when to prescribe empiric broad-spectrum therapy for suspected infection due to MDR pathogens is the de-escalation approach. Knowledge of patient risk factors for the presence of infection with antibiotic-resistant or MDR pathogens, such as those outlined in Table 1, should be routinely sought as part of antibiotic decision-making, and can be employed in a de-escalation algorithm [17]. Clinicians in the ICU should then weigh the potential benefit versus harm of starting empiric therapy targeting MDR pathogens, recognizing that there is little room for error when dealing with patients who have severe sepsis or septic shock [3]. Most importantly, adequate clinical specimens should be obtained for microbiologic processing prior to starting antimicrobial therapy in order to identify the etiologic agent(s) of infection and allow the use of narrower spectrum antibiotics. Another important factor that must be taken into account is the duration of antibiotic therapy. Shorter courses of antibiotic exposure are less likely to promote the emergence of antibiotic resistance, thus early discontinuation of antibiotics based on microbiology results, biomarkers such as procalcitonin, and the clinical course of the patient should be carefully taken into account.

For the future, a number of novel methods aimed at improving the early identification of pathogens and related antibiotic susceptibilities are on the horizon and will improve antibiotic decision-making for critically ill patients. These approaches include the use of molecular methods (e.g., PCR, electrospray ionization mass spectrometry, and MALDI-TOF) as well as advanced automated microscopy techniques that allow the identification of bacterial species and resistance genes, as well as the identification of direct bacterial killing. It is expected that these technologies could become available for routine use over the next 5 years. However, the costs associated with their use will undoubtedly limit their overall utilization in many hospitals. Therefore, intensivists should develop and routinely employ an antibiotic decision-making practice in the ICU that employs locally acceptable, or ideally locally validated, risk factors for MDR infection as part of an overall de-escalation strategy.

Compliance with ethical standards

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