Empiric Antibiotic Prescribing for Suspected Sepsis: A Stewardship Balancing Act

The optimal approach to empiric antibiotic prescribing for suspected sepsis in the emergency department (ED), specifically timing and spectrum of therapy, is a matter of significant ongoing controversy.[1−3] The debate hinges on interpretation of the ratio between benefit from prompt, active antibiotic therapy for patients with bacterial sepsis and the established societal (e.g. selective pressure towards bacterial resistance) and patient level harms associated with unnecessary antibiotic therapy (e.g. adverse drug reactions, *Clostridiodes difficile* infection).

In this issue of *AJMS*, Oxman et al.[4] examine the rate of multidrug resistant bacteremia among ED patients with suspected sepsis and discuss the results in relation to the optimal approach to empiric prescribing of antibiotics. We commend the authors for contributing to such a critically important antibiotic stewardship topic. Their concluding statement that "the overall number of infections due to MDR bacteria was low [12%]" merits additional commentary. This single center finding (2012−2013) is very similar to a recent cohort study involving 104 US hospitals (2009−2015) which identified the overall prevalence of resistant gram-positive and gram-negative organisms in culture confirmed sepsis to be 13.6% and 13.2% respectively.[5] Interestingly, these data conflict with a previous report involving 38 tertiary care hospitals and 68 small community hospitals (106 total, 1999−2012) that identified an overall resistance rate of 30% among outpatient (including ED) blood culture samples.[6] These results should also be considered in relation to the Antibiotic Resistance Threats in the United States report, released by the Centers for Disease Control and Prevention in late 2019, that demonstrated rising rates of infection due to extended-spectrum beta-lactamase (ESBL)-producing Enterobacteriaceae between 2012−2017.[7]

Acknowledging the margin of error inherent in prevalence estimates and the various time periods included in these studies, the pooled results suggest it is reasonable to assume somewhere between 1/8th to 1/3rd of culture confirmed septic ED patients have a MDR infection. This supports the argument for rapid, broad-spectrum empiric therapy for all patients with suspected sepsis, particularly those with meeting criteria for severe sepsis or septic shock, based on observational studies demonstrating an increased risk of mortality with each hour of delay in active antibiotic administration.[8,9] These studies formed the basis for the Surviving Sepsis Campaign's Hour-1 Bundle which in part calls for administration of broad-spectrum antibiotics within 1 hour of sepsis recognition.[10] Additionally, this practice was codified in 2015 by the US Centers for Medicare and Medicaid Services (CMS) Severe Sepsis and Septic Shock Early Management Bundle (SEP-1), a publically reported, "all-or-nothing" ED metric that in part requires broad-spectrum antibiotic administration within 3 hours of sepsis onset.[11]

Of course focusing only on the potential benefit for patients with sepsis ignores the societal impact and risk of harm to individual patients when antibiotic therapy is overly broad-spectrum or altogether unnecessary (e.g. conditions that mimic sepsis).[12] Both the Hour-1 bundle and SEP-1 metric have generated significant opposition from those who accurately point out that they exert pressure on ED clinicians to initiate broad-spectrum antibiotics for clinically stable patients who meet nonspecific sepsis criteria that often result in overdiagnosis.[3,13] Also, it is important to note that other analyses, including a meta-analysis, examining time to antibiotics in sepsis have yielded conflicting results and there are ongoing concerns about potential biases in the available observational studies (e.g. varying definitions of time zero).[1,14]

With no clear means to resolve the conflicting viewpoints regarding the optimal empiric prescribing approach for patients with suspected sepsis, it is best to focus on antibiotic stewardship strategies that strike a balance between aggressive and judicious prescribing. We propose the following present and future opportunities for ED clinicians to improve their probability of correctly identifying the causative organism or presence of sepsis and thus enabling more effective tailoring of empiric antibiotic therapy or elimination of unnecessary antibiotics altogether.

In the SEP-1 era, early administration of broad-spectrum antibiotics is the standard for ED sepsis care. In an effort to improve compliance, hospitals may implement protocols requiring immediate antibiotic therapy once sepsis criteria are met, even in the presence of an incomplete workup and/or diagnostic uncertainty. In a recent position paper, the Infectious Diseases Society of America has advocated an alternative approach, including limiting SEP-1 reporting to patients with septic shock and letting care for patients with suspected sepsis without shock (i.e. stable) be guided by the treating clinician with support from evidence based guidelines.[3] This approach would enable ED clinicians to first focus on source identification and control, when applicable, in stable patients. The brief delay needed to obtain a comprehensive history and physical exam, review previous culture data, and obtain necessary diagnostic tests (e.g. chest radiograph, urinalysis) may be justified if a more accurate source is identified and overly broad antibiotics can be safely avoided.[15] Patients with no clear source of infection or evidence of deterioration could then be initiated

on broad-spectrum empiric therapy without further delay. The actual choice of empiric antibiotic therapy should always be informed by local resistance patterns. Provided an ED has sufficient volume, an ED-specific antibiogram will provide the most accurate assessment of local bacterial resistance patterns by infection type and facilitate optimal empiric antibiotic selections. Also, emerging literature suggests traditional antibiograms can be successfully augmented with multivariate resistance prediction models to improve empiric therapy and time to de-escalation.[16]

ED clinicians often treat suspected sepsis with antibiotics only to later learn that the non-specific systemic inflammatory response syndrome (SIRS) criteria were the result of a non-infectious mimic or viral illness (e.g. influenza or SARS-CoV-2). While secondary bacterial infections do rarely occur, the combination of clinical acumen and a positive rapid viral pathogen diagnostic assay can significantly lower the probability of bacterial sepsis. In clinically stable patients with both sepsis criteria and positive viral assay result, ED clinicians should engage in shared decision-making with patients and coordinate care with receiving providers (e.g. primary care provider or hospitalist) in an attempt to avoid the unnecessary initiation of antibiotics.

While the opportunity to tailor antibiotic therapy based on culture and susceptibility results is not traditionally available to ED clinicians, this paradigm is rapidly changing as emerging biomarker, host immune gene expression and microbiology-based point-of-care technologies continue to improve the accuracy of sepsis diagnosis and reduce the time to pathogen identification.[17,18] Once validated and disseminated, these novel technologies will help to differentiate true sepsis from mimics and facilitate optimal empiric antibiotic selection and early de-escalation so that the use of broad-spectrum agents can be minimized.

In summary, we agree with the authors that routine use of broad-spectrum antibiotics for all clinically stable patients with suspected sepsis should be revisited. Fortunately, there are ongoing advocacy efforts to counter drivers of antibiotic overuse in clinically stable ED patients with sepsis criteria (SEP-1) and available clinical strategies that can improve empiric prescribing when indicated. Finally, the future is very promising in terms of emerging technologic solutions that have the potential to render this entire dilemma obsolete.

Michael Pulia, MD, MS*
Robert Redwood, MD, MPH
Department of Emergency Medicine, University of Wisconsin-Madison School of Medicine and Public Health, Madison, WI, USA

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