Antibiotic Thresholds for Sepsis and Septic Shock

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(See the Major article by Cressman et al on pages 930–7.)

In this issue of the journal, Cressman et al describe the antibiotic coverage thresholds that clinicians are willing to accept for the treatment of patients with sepsis of varying disease severity [1]. In general, they observed that illness severity and infectious diseases specialty predicted higher thresholds of coverage, whereas less clinical experience and lower self-reported prescribing intensity predicted lower thresholds of coverage. These findings are of particular interest and relevance given recent recommendations for the treatment of patients with sepsis employing standardized treatment bundles. Retrospective and time-series studies suggest that the use of treatment bundles for the management of sepsis and septic shock can be associated with lower hospital mortality potentially because of earlier administration of antibiotics [2–4]. However, these treatment bundles typically fail to examine important antimicrobial management issues including whether antibiotic therapy is necessary in all patients with presumed sepsis, the dosing strategies and duration of antibiotics, and whether the administered antibiotic regimen has in vitro activity against the offending pathogens. Nevertheless, studies of treatment

bundles for sepsis serve, in part, as justification for the authors of the Surviving Sepsis Campaign Guidelines to recommend the use of broad-spectrum antibiotics within 1 hour of presentation in all patients with sepsis [5].

Other prospective studies of sepsis treatment bundles and educational interventions that reduce time to antibiotic administration have failed to demonstrate similar improvements in outcomes [6–8]. In addition, a systematic review and meta-analysis found no mortality benefit with the administration of antibiotics within 3 hours of emergency department triage or 1 hour of shock recognition among patients with severe sepsis or septic shock [9]. This may be due to several factors including patient severity of illness, pathogen and antibiotic susceptibility patterns, an already high level of medical care provided at baseline prior to implementation of the intervention, and difficulty establishing an accurate and validated “time zero” for gauging the impact of sepsis therapies. One recent study highlighted that abstractors’ agreement on time zero occurred only 36% of the time [10]. It seems intuitive that earlier administration of antibiotics would be more likely to demonstrate benefit in patients with true infection as opposed to noninfectious causes of sepsis (eg, drug reactions, pancreatitis, trauma, aspiration pneumonitis), in patients with shock, and individuals with compromised immune systems. We know that even when appropriate early antibiotic therapy is administered to infected patients, those in shock have a greater mortality than patients

without shock and organ dysfunction [11]. Moreover, recent studies have demonstrated that earlier or broader antibiotic therapy may not result in improved outcomes for infected patients from the community setting, those with lower severity of illness, or individuals coming from areas with a low overall burden of antibiotic-resistant pathogens [12–14].

A recent editorial has attempted to focus attention on the problems associated with the overuse of antibiotics in patients with possible sepsis [15]. That editorial highlights the difficulties in establishing an accurate diagnosis of sepsis attributed to underlying infection, the adverse consequences associated with routine administration of antibiotics in critically ill patients, and the problem of equating sepsis with the more severe condition of septic shock. Recent pleas have emerged from the Infectious Diseases Society of America, emergency medicine thought leaders, and critical care thought leaders urging for more rationale approaches for directing antibiotic therapy in complex patients and eliminating the 1 hour sepsis bundle [16, 17]. Rapid molecular diagnostics (RMDs) seem to be well positioned for expediting the evaluation of patients with sepsis and septic shock in order to insure that effective early antibiotic therapy is administered as well as to avoid the unnecessary use of broad-spectrum agents [18].

The mechanisms explaining poorer clinical outcomes when infection occurs due to antibiotic resistant bacteria is not completely clear. In general, these bacteria are not believed to be inherently

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more virulent than their susceptible counterparts. This is supported by a study of bacteremic pneumonia showing that *Enterobacteriaceae* were most likely to receive initially inappropriate antibiotic therapy (ie, an initial regimen without demonstrable in vitro activity against the offending pathogens), whereas infection with *Pseudomonas aeruginosa* was associated with the greatest mortality [19]. The greater mortality with *Pseudomonas aeruginosa* infection was presumably related to the intrinsic virulence properties of the pathogen [20]. Unfortunately, antibiotic resistance and its rapid evolution have made efforts to insure the delivery of appropriate therapy more difficult, and appropriate therapy is a key determinant of outcome in severe infections [21, 22]. The administration of appropriate therapy has consistently been associated with lower mortality in sepsis and septic shock [6, 23–25]. The opportunity for RMDs to improve patient outcomes, especially mortality, may be greatest in sicker patients including those with septic shock and individuals at risk for infection with antibiotic resistant pathogens. Indeed, cost considerations, local susceptibility patterns, and hospital case-mix will likely be important considerations for institutions when deciding how to incorporate RMDs into their management of sepsis and septic shock.

The main challenge for clinicians is deciding when to treat patients with presumed sepsis with antibiotics and the selection of a specific regimen. Current recommendations suggest that sicker patients, including those with shock, should receive broad-spectrum therapy due to the greater potential risks involved with inappropriate treatment [26, 27]. However, the presence of shock does not necessarily reflect greater likelihood for receiving inappropriate therapy and may simply be a reflection of the pathogen's virulence or host factors [19, 20, 28]. Attempts to avoid the prescription of broad-spectrum antibiotics have had mixed success. For example, a recent

Figure 1. Proposed matrix to help guide empiric antibiotic prescribing in patients with possible sepsis.

randomized trial among patients with *Escherichia coli* or *Klebsiella pneumoniae* bloodstream infection and ceftriaxone resistance found that definitive treatment with piperacillin-tazobactam compared with meropenem did not result in noninferior 30-day mortality [29]. Patients receiving piperacillin-tazobactam had a statistically greater mortality compared with patients treated with meropenem. This study highlights the importance of early identification of antibiotic resistance to optimize antimicrobial prescription in order to improve patient outcomes. In the absence of immediate dissemination and implementation of RMDs, clinicians can also use previous culture results in their selection of empiric regimens, as prior resistance is highly specific for current resistance to a particular antibiotic [30].

Using Figure 1, we present informative examples of empiric antibiotic prescribing. Consider a patient admitted to the hospital ward with a low acuity of illness, minimal risk factors for antibiotic resistance, and a clinical presentation for which infection is on the differential diagnosis but not the most likely cause. This patient would correspond to the gray cube in Figure 1—a patient in which antibiotics could likely be avoided while waiting for diagnostic testing. On the other hand, consider a patient admitted

to the intensive care unit in shock with significant risk factors for antibiotic resistance, corresponding to the black cube in Figure 1. Such a patient would fall into the category of potentially needing broad-spectrum antibiotic therapy up front, guided by the local antibiogram, available RMDs, and the patient's previous culture results.

In summary, Cressman et al present an interesting first step toward understanding the landscape of attitudes in empiric antibiotic prescribing among Canadian internal medicine and infectious diseases physicians. Further work is needed to understand their work in a broader context that includes other front line antibiotic prescribers. Empiric antibiotic prescribing will continue to be a moving target, but with advances in RMDs, the ideal scenario of minimizing antibiotic use while maximizing excellent patient outcomes moves closer to realization, including in critically ill patients [31].

Notes

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