Editorial

Continuous infusion of beta-lactams: a blissful option for the intensive care unit

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Antimicrobial resistance remains a growing threat in the care of critically ill patients. Many pathogens previously susceptible to common antibiotics are now resistant to those agents. This pattern exists for both gram-negative and gram-positive organisms. In intensive care units (ICUs) in the United States more than 60% of all isolates of *Staphylococcus aureus* are methicillin-resistant (1). In Europe, Asia, and the US, many enterobacteriaceae produce extended-spectrum beta-lactamases (ESBLs) which hydrolyze some anti-infectives and which render them resistant to all but carbapenems. Beyond ESBLs, select pathogens are now resistant to carbapenems as well. The prevalence of these carbapenem-resistant enterobacteriaceae (CREs) has more than tripled in Europe since 2010 (2). The situation is no better for *Pseudomonas aeruginosa* (*P. aeruginosa*) or Acinetobacter. For example, more than 50% of Acinetobacter are non-susceptible to carbapenems (3). Similarly, among *P. aeruginosa*, Micek *et al*. reported that 30% of such organisms recovered in ventilator-associated pneumonia in a cross section of 12 ICUs globally met criteria for multi-drug resistance (4).

These increasing rates of resistance have forced clinicians to intensify their empiric use of broad-spectrum antibiotics. Physicians have come to recognize that the most important determinant of outcomes in severe infection is the timeliness and appropriateness of initial antibiotic therapy. Multiple analyses have documented that failure to prescribe an anti-infective that is *in vitro* active against the culprit pathogen in a timely manner increases the risk for death up to 4-fold (5,6). More specifically, some estimate that the number needed to treat with appropriate therapy (as compared to delayed and/or inappropriate therapy) in order to prevent one death in the setting of severe infection may be as low as seven (7). Furthermore, the strongest risk factor for receiving inappropriate therapy is the presence of an infection due to an MDR pathogen (8). In other words, when the culprit organism is susceptible to a commonly used antibiotic, initial appropriate therapy is almost guaranteed so long as the infection is recognized soon after onset. Conversely, if resistance is present, it becomes possible for the clinician to opt for a therapy that may be no better than placebo. This observation is confirmed by the fact that in cases series of pan-resistant infection, mortality rates (60–70%) rival those noted in the pre-antibiotic era.

Of course, striving to deliver appropriate therapy via relying on the use of ever-broader antibiotic therapy only serves to promote further resistance. Unnecessary use of these broader agents creates selection pressure so that resistant isolates preferentially lead to either colonization or super-infection. Greater reliance on broader agents also may promote resistance not only to the specific antibiotic being prescribed but also to other classes of agents. In short,

a vicious cycle exists that is spiraling out of control.

Experts have suggested several strategies for combating this conundrum. First, use of rapid diagnostic technologies could lead to the more rapid narrowing or discontinuation of antimicrobial therapy. Although theoretically appealing, rapid diagnostics do not necessarily help the clinician sort colonization from infection, particularly in the setting of pneumonia. Moreover, results from rapid diagnostic testing can only be interpreted in the context of understanding the pre-test probability for the presence of a resistant pathogen (9). Second, shortening the course of antibiotic therapy can decrease antibiotic use. New guidelines for nosocomial pneumonia specifically endorse this approach (10). Enforcing shorter treatment durations, however, will require a substantial change in physician culture and training—and hence is not as easy as some would suggest. Third, researchers are striving to create and test novel agents with activity against many of the most resistant pathogens such as CREs and Acinetobacter. Unfortunately this approach of engineering ourselves out of the problem faces multiple hurdles. It is also fraught with uncertainty and risk. Fourth, some advocate that a better appreciation of the principles of pharmacodynamics (PD) and pharmacokinetics (PK) could enhance outcomes.

PD correlates the concentration of the antibiotic with its ability to kill or inhibit the target pathogen, while PK describes the concentration-time profile of an antibiotic. Tying these concepts together allows one to appreciate that the way in which a drug is dosed and delivered affects its ability to kill bacteria. For example, the killing activity of some agents such as aminoglycosides is a function of the peak concentration of the drug (Cmax) relative to the minimum inhibitory concentration (MIC) of the pathogen. Other agents, such as beta-lactams, cephalosporins, and carbapenems exert their killing as a function of the time interval for which the concentration of the agent is above the MIC of the pathogen (e.g., T > MIC).

Conventionally, beta-lactams are administered in a bolus so that the drug is given rapidly over 30 to 60 minutes. This approach fails to optimize the PK PD relationship for these antibiotics. As such, it undermines the potential efficacy against higher MIC organisms. For lower MIC organisms, a bolus approach may be sufficient. However, the current and continuing threat arises from the MDR organisms that, by definition, have higher MICs to commonly utilized antibiotics.

In a recent trial testing the hypothesis that that extended infusion of beta-lactams would improve patient outcomes, Abdul-Aziz *et al*. sought to document the potential value for an extended infusion paradigm (11). The Beta-Lactam Infusion in Severe Sepsis (BLISS) trial was conducted at two sites and randomized patients to various infusion strategies. Readers should note that BLISS represents the most recent trial in a series of ever expanding studies to address the role for PK PD in the management of severe infection. In fact, a recent meta-analysis of three randomized trials comparing intermittent *vs*. continuous infusion (CI) of beta-lactams suggested that CI reduced mortality and improved clinical cure rates (12). Earlier trials of PK PD optimization via reliance on continuous beta-lactam infusion suggested but did not document improvements in clinically meaningful endpoints. These studies did demonstrate that CI improved rates of achieving goal PK targets (e.g., T > MIC), but failed to convincingly justify the excess effort required for CI (12).

BLISS, unlike earlier reports and meta-analyses, significantly improves upon our appreciation of PK PD issues in severe sepsis and documents, for the first time in a single trial, the clinical value of continuous beta-lactam infusion. Not blinded for practical reasons, BLISS randomized 140 subjects to the different administration options (11). Cure rates were nearly 65% higher in patients receiving CI beta-lactams (11). Not surprisingly, the probability of reaching PK targets was significantly higher in the CI arm. In fact, with intermittent bolus fewer than 70% of subjects reached the target PK parameter (11). The trial was not powered to detect differences in mortality and, as such, mortality rates were similar between the two dosing paradigms. Nonetheless, patients randomized to CI spent fewer days on mechanical ventilation. Any increase in ventilator-free days (VFDs) is both clinically and economically important.

Although BLISS represents a crucial and important advance, the study has a number of limitations. First, as noted above, the trial was not blinded. This could have confounded efforts to assess clinical cure rates. Second, investigators did not identify a pathogen in every subject. This lack of pathogen identification forced the investigators to make certain assumptions regarding the MICs of these "missing" organisms. Moreover, there was an imbalance in both the primary infection site (pneumonia was fully 15% more common in the CI arm) and the rate of documented pathogen recovery with fewer organisms identified in the CI arm (11). Third, there was no standardized approach to ventilator weaning between the two sites. This could have indirectly affected differences in VFDs. Finally, the BLISS protocol did not specify the beta-lactam antibiotic to be utilized by the treating physician. Therefore, some subjects

received piperacillin/tazobactam while others were treated with cefepime or meropenem. Failure to control for the type of beta-lactam infused may improve the generalizability of the researchers' findings, but it comes at the potential cost of further confounding.

One question that remains unanswered by BLISS is the prevalence of resistance one must be facing in order for a CI option to prove useful. If rates of beta-lactam resistance are low, and thus so are the MICs encountered for various pathogens, then a CI strategy likely offers little. The key issue is the relationship between the infusion duration and the MIC. If the denominator in this relationship is low (e.g., the MIC), then CI should not theoretically offer much benefit.

Despite these limitations, BLISS represents an important trial for those who care for critically ill subjects. Since a CI strategy did not increase rates of adverse events and since it is not necessarily associated with increased cost, reliance of CI for beta-lactams represents a relatively simple way to potentially improve patient outcomes without compromising other concerns. Other recommendations for addressing antibiotic resistance either require the purchase of new, expensive diagnostic tests of unclear value or outlays for costly novel antibiotics. BLISS demonstrates that we need not to succumb immediately to these pressures. Rather, a smarter, more scientific approach to drug dosing can help us to combat drug resistance. The evolution in our appreciation of PK and PD in the ICU has come methodically and slowly. However, BLISS demonstrates that it has been worth the wait.

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Footnote

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