Commentary

Is there a role for continuous infusion of β-lactam antibiotics in severe sepsis?

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Sepsis is a leading cause of mortality and morbidity in critical care (1,2). There is an expanding literature examining optimal administration of β-lactam antibiotics in critically ill patients (3,4). The bactericidal and broad spectrum nature of β-lactams make them attractive in patients with sepsis. The time-over-MIC dependent killing with β-lactams would suggest benefit with administration as continuous infusion instead of intermittent dosing, particularly given the fluid shifts that occur in critically ill patients (5-7). Meta-analysis of studies comparing continuous infusions of β-lactams to standard intermittent dosing in acute infections have failed to find a consistent clinical benefit in mortality, infection recurrence, clinical cure, super-infection post-therapy, and safety outcomes in both critically- and non-critically ill patients (3,4,8-10). The question remains whether patients with severe sepsis will benefit (11).

Dulhunty *et al*. (the BLING II investigators) recently published "*A multicenter randomized trial of continuous versus intermittent β-lactam infusion in severe sepsis*", in a heterogenous critically-ill population (7). This was a well done, double-blinded, randomized (with good allocation concealment), controlled pragmatic trial conducted in 25 intensive care units in Australia, New Zealand, and Hong Kong, in adults with severe sepsis who were already being treated with a β-lactam antibiotic for <24 hours (median about 12 hours). The primary outcome was alive ICU-free days determined at day 28 after randomization; sample size was calculated to have 90% power to detect a difference of 3 days with α of 0.05. Secondary outcomes included: day-90 mortality, clinical cure at day 14 after antibiotic cessation, alive organ failure-free days at day 14, and duration of bacteremia post-randomization. The most common β-lactams used were piperacillin-tazobactam (69.3% continuous infusion, 71.4% intermittent infusion), and meropenem (29.7% continuous infusion, 27.3% intermittent infusion). Patients were well balanced in characteristics at baseline, and patients received the blinded study drug for a median of 3–4 days (until intensive care unit discharge). There was no difference in alive ICU-free days (18 *vs*. 20 days; P=0.38), in 90-day survival (74.3% *vs*. 72.5%; hazard ratio, 0.91; 95% CI, 0.63–1.31; P=0.61), clinical cure (52.4% *vs*. 49.5%; odds ratio, 1.12; (95% CI, 0.77–1.63; P=0.56), organ failure-free days (P=0.27), or duration of bacteremia (P=0.24), hospital length of stay, or adverse events between groups on intention to treat analysis.

This is the largest multicenter trial aiming to determine clinically relevant outcomes with continuous *vs*. intermittent infusion of broad spectrum β-lactam antibiotics in severe sepsis. Previous studies have found higher β-lactam serum concentrations with continuous infusion in critically ill patients with severe sepsis (12). The question has been whether this surrogate outcome translates to patient-relevant clinical benefit (11). There are reasons to think that it should be beneficial. For example, there is evidence that tissue levels of β-lactams in critically ill patients are lower than predicted from serum levels, and may be higher with continuous infusion (13-15). Given that β-lactams are hydrophilic, have a small distribution volume similar to extracellular water, and are predominantly excreted via the kidneys, one might expect a higher extracellular tissue level in critically ill patients who have capillary leak (resulting in expanded extracellular space) receiving continuous infusions (5,15). So, why might Dulhunty *et al*. not have found benefit to continuous infusion of β-lactams?

First, most patients in this study had lungs as infection source. In ventilator associated pneumonia (VAP) it is difficult to determine the organisms responsible for the infection, and it is possible that β-lactams were not optimal therapy for some. There is no clear gold-standard for diagnosis of VAP, and it is also possible that some of the patients may not have had sepsis at all. Second, most patients did not have bacteremia (81%), making it difficult to determine the responsible pathogen(s) and their MICs, particularly in patients who may have received their first doses of antibiotics prior to cultures (16). Third, the majority of the bacterial isolates were susceptible to the β-lactam used. With rising prevalence of more resistant gram-negative bacilli a benefit from continuous infusion of β-lactams to achieve longer time-above-MIC may emerge (2). Fourth, there is question whether continuous infusion of piperacillin-tazobactam actually achieves higher time-above-MIC than intermittent dosing (12). Future studies may consider a role for therapeutic drug monitoring to demonstrate differences between groups (5,12,14,15). Finally, those with septic shock may be a subgroup most likely to benefit from continuous infusion of β-lactams. There were many excluded patients, including those who had received antibiotics for >24 hours, and those where there was inability to randomize or prepare study medication, which may have excluded patients with the most severe sepsis and septic shock (14,15). Nevertheless, the results are similar to the previous BLING II study examining pharmacokinetics; in that trial, survival to hospital discharge was 90% in continuous *vs.* 80% in intermittent β-lactam infusion groups (P=0.47) (12). This previous trial had better clinical cure and survival outcomes; this may be explained by the higher severity of illness (including use of renal replacement therapy in 26% of patients) and fewer days on randomized therapy (3 *vs.* 5 days) in the current trial.

Where do we go from here? There are patient groups that may deserve further study. First, the growing population of patients with sepsis caused by gram-negative bacilli with increasing resistance patterns (1,13). Clearance of bacteremia in such patients is important, and longer duration of serum β-lactam levels >4× MIC provides optimal bactericidal effects. To safely achieve this with increasingly resistant gram negative pathogens, a continuous infusion may be required, particularly in those who have persistent bacteremia (5,14). Second, infections where tissue antimicrobial levels are more difficult to achieve, including meningitis, intra-abdominal abscess, and lung abscess (14). Third, patients very early in their episode of sepsis, with antimicrobials started in the first hour of presentation when there is highest likelihood of improving outcome (1). Finally, therapeutic drug level monitoring in patients with a known pathogen may allow determination of whether optimal pharmacodynamics are obtained in either group, and the relationship to clinical outcome (17,18).

At this time we do not suggest use of continuous infusion of β-Lactams in critically ill patients with severe sepsis. This is supported by the results of this trial, and previous meta-analyses (3,8-10). Further study may be required to define subgroups of patients that may benefit. A role for therapeutic drug monitoring of β-Lactams targeting time-above-MICs may be on the horizon (14).

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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