**Sepsis** describes life-threatening organ dysfunction due to a dysregulated host response to infection. It is a global health priority affecting 55 million people worldwide causing 11 million deaths annually.1 Failure to initiate timely antibiotic therapy for sepsis can result in progression to septic shock, which is associated with a mortality rate of 30% to 40%.2 Accordingly, sepsis is recognized as a time-critical medical emergency.

Current management focuses on “bundles”3 of care incorporating early recognition, timely antibiotic administration, and fluid resuscitation. Two commonly prescribed antibiotics for empirical treatment of sepsis are the β-lactams piperacillin-tazobactam and cefepime. Both provide broad in vitro activity against gram-positive and gram-negative organisms, including *Pseudomonas aeruginosa*. They are often used in combination with vancomycin to include activity against methicillin-resistant *Staphylococcus aureus*.

Both β-lactam antibiotics are associated with risk. The purported increased risk of acute kidney injury (AKI) from the combination of piperacillin-tazobactam plus vancomycin compared with other β-lactam agents has led to a cultural shift away from the empirical use of piperacillin-tazobactam among many prescribers. Meta-analyses of observational studies found vancomycin plus piperacillin-tazobactam is associated with greater incidence of AKI with odds ratios (ORs) of up to 3.64 and an absolute AKI incidence of 22.2% compared with 12.9% in comparators.5 Based on these data, the US Food and Drug Administration warns that coadministration of piperacillin-tazobactam with vancomycin may increase the incidence of AKI.

However, whether this association reflects actual kidney damage has been questioned,6 and key flaws in the retrospective observational studies include the reliance on serum creatinine level as the measure of AKI, unmeasured confounding, and some inconsistencies across studies. Animal studies7,8 and a recent prospective clinical study9 suggest that increases in serum creatinine level may reflect inhibition of tubular secretion of creatinine without underlying kidney injury. Levels of kidney injury biomarkers such as kidney injury molecule 1 and cystatin C are not increased when administration of vancomycin plus piperacillin-tazobactam is compared with either drug alone or the combination of vancomycin plus cefepime.

Cefepime has been associated with neurotoxicity including altered mental status, myoclonus, and nonconvulsive seizure epilepticus.10 The risk for cefepime neurotoxicity appears to be increased with kidney dysfunction and higher cefepime exposures, usually described as elevated trough serum concentrations. Because kidney dysfunction is common in patients with sepsis, some fear use of cefepime may precipitate delirium in an already tenuous population.

In this issue of *JAMA*, Qian and colleagues11 provide needed randomized clinical trial evidence to guide empirical prescribing for patients presenting to the emergency department with suspected sepsis. In this single-center, pragmatic, open-label, randomized clinical trial, Qian and colleagues11 sought to determine whether use of piperacillin-tazobactam or cefepime for empirical sepsis treatment affects the risks of AKI or neurological dysfunction. They enrolled 2511 patients almost exclusively in the emergency department (95%). At baseline, 54% of participants met sepsis criteria, 13% required vasopressors, and 8% required mechanical ventilation.

The primary outcome of highest stage of AKI or death by day 14 did not significantly differ between the cefepime group and the piperacillin-tazobactam group (OR, 0.95 [95% CI, 0.80-1.13], *P* = .56).11 The primary outcome result was consistent across the adjusted and prespecified sensitivity analyses. There were no differences in the incidence of major adverse kidney events by day 14 between the groups. The day 14 mortality rates were similar (7.6% in the cefepime group vs 6.0% in the piperacillin-tazobactam group).11 The methods defining baseline kidney function and AKI were robust. Because more than 80% of the population received at least 1 dose of vancomycin, this trial provides the highest quality evidence to date to show there is no difference in the incidence of AKI between use of piperacillin-tazobactam and vancomycin vs cefepime and vancomycin.

Patients in the cefepime group had fewer days alive and free of delirium and coma within 14 days with a mean difference of 0.3 days (OR, 0.79 [95% CI, 0.65-0.95]).11 The significant difference was only observed in patients with confirmed sepsis, whereas there was no difference in delirium in patients without confirmed sepsis. It is unclear what the distribution of delirium and coma was between medical ward and ICU patients. Delirium management practices were not standardized; however, the use of analgesia and sedation at baseline was similar across both groups.

There are limitations to the trial.11 It was a single-center study. Participants received a short duration of antibiotic treatment (median, 3 days [IQR, 1-4 days]) and nearly 50% did not actually have sepsis. Events occurring in the latter part of the key follow-up time point of 14 days are less likely to be directly attributable to the antibiotic received within the first 5 days. Thus, we cannot extrapolate the findings to ongoing therapy with combinations of vancomycin with piperacillin-tazobactam and cefepime.

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There was significant crossover of antibiotic received (19% in the cefepime group and 17% in the piperacillin-tazobactam group). It is not clear why some patients received both drugs despite electronic health record alerts reminding clinicians about the trial. Of the patients still receiving antibiotics by day 7, approximately one-third were receiving the alternative drug to which they had been assigned. Thus, the intervention groups are not as clean as desired.

As an unblinded open-label study, there is potential for bias in the ascertainment of the outcomes. Are participants known to be receiving piperacillin-tazobactam or cefepime more likely to have investigations for AKI and neurotoxicity, respectively? In addition, there is a between-group difference of 0.3 days alive and free of delirium and coma within 14 days clinically significant?

The dosing regimens for both piperacillin-tazobactam and cefepime may not reflect broader clinical use. Piperacillin-tazobactam was intravenously administered with a dose of 3.375 g every 8 hours in the trial as a 4-hour infusion. However, dosing would typically be at a higher dose of 3.375 to 4.5 g every 6 hours over 30- to 240-minute infusions, particularly because the 2023 Clinical Laboratory Standards Institute and European Committee on Antimicrobial Susceptibility Testing base their clinical breakpoints on these higher doses.12,13

Importantly, cefepime was administered via rapid intravenous push, which is associated with enhanced toxic effects compared with intermittent or extended infusions.14,15 Thus, the dosing regimens may have reduced the risk of AKI with piperacillin-tazobactam due to the lower dose used and exaggerated the risk of neurotoxicity with cefepime due to the rapid intravenous push.

Optimal empirical therapy for sepsis is extremely challenging, especially because regulatory bodies strive to derive protocols for an infectious syndrome that is heterogeneous and phenotypically diverse.16 The trial by Qian and colleagues13 does not describe whether patients had an identified pathogen (ie, confirmed infection), and if so, whether the patients received in vitro empirical therapy, which makes the results challenging to generalize for infection treatment. However, because institutions must make decisions about which antibiotics to position on medical wards for rapid administration in patients meeting sepsis criteria, these data should offer solace that if the choice is made to use piperacillin-tazobactam, there is not an increased risk of AKI.

Antibiotic choice is multifactorial. First, effectiveness and safety must be considered. In the absence of clinically significant safety differences, the selected antibiotic should be the one with the highest probability of in vitro activity against the institution’s most common causative pathogens.

Second, product availability and storage are crucial operational considerations. Frozen products cannot be readily positioned in emergency departments, whereas premixes (compounds with extended stability) or minibag plus systems can be stored, which may guide antibiotic selection if effectiveness and safety are otherwise equal. In addition, practical matters such as dosing frequency and the effects on nursing workforce time are meaningful considerations.

Overall, we commend Qian and colleagues13 for conducting an elegant, pragmatic trial embedded within an electronic health record. By applying the principle of randomization, the authors address an important controversy regarding empirical antibiotic use. With the caveats mentioned above, they demonstrate that piperacillin-tazobactam does not increase the risk of AKI compared with cefepime.

The trial design facilitated rapid enrollment for a traditionally difficult to enroll population by embedding the trial within routine care. This should be applauded. Qian and colleagues13 provide a roadmap for such embedded randomized clinical trials for empirical antibiotic treatment of sepsis. The current study13 could be replicated using almost identical processes at multiple hospitals. Now, the question of whether antibiotics with antipseudomonal activity are even required for community-acquired and low-acuity sepsis can be addressed.

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