Cefazolin or nafcillin? —a commentary on the optimal treatment of methicillin-susceptible *Staphylococcus aureus* bacteraemias: a meta-analysis of cefazolin versus antistaphylococcal penicillins

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Staphylococcus aureus bacteremia represents significant burden on the healthcare system with early mortality rates as high as 60% and more recent studies suggesting mortality rates of 10–30% (1,2). While methicillin-resistant *Staphylococcus aureus* (MRSA) has garnered much of the attention due to higher mortality rates and treatment difficulties, the optimal treatment of methicillin-susceptible *Staphylococcus aureus* (MSSA) is still in question (1). Historically, antistaphylococcal penicillins (ASPs) such as nafcillin, oxacillin, cloxacillin, and flucloxacillin and first-generation cephalosporins, such as cefazolin, have been considered the treatment of choice for infections caused by MSSA (3-7). We read with interest the meta-analysis from Bidell and colleagues comparing ASPs to cefazolin for the treatment of MSSA bacteremia in adults (8). Over 4,300 patients were included in this analysis. The study concluded that cefazolin was associated with a lower 90-day all-cause mortality [odds ratio (OR) 0.63, 95% confidence interval (CI): 0.41–0.99] and a lower rate of treatment associated adverse events (OR 0.25, 95% CI: 0.11–0.56), though no difference in clinical failure was detected (OR 0.85, 95% CI: 0.41–1.76) (8). The authors rightfully urge caution due to the uncontrolled and retrospective nature of the included studies. While this study has re-sparked interest in the optimal antimicrobial for MSSA bacteremia, the debate between ASPs and cefazolin dates back decades to the 1970's.

In 1975, Sabath and colleagues published a report evaluating the inoculum effect on the antimicrobial activity of ASPs and cephalosporins of beta-lactamase (Bla) producing strains of MSSA. It was shown that ASPs were more resilient to beta-lactam degradation by hydrolytic enzymes than cephalosporins (9). Simply put, the inoculum effect demonstrates that higher concentrations of colony forming units (CFU)/mL (10^7 CFU) result in higher minimum inhibitory concentrations (MIC). Further animal models conducted in the 1970's and 1980's were conflicting with some studies supporting the inoculum effect and others failing to replicate previous findings (10-14). As such, guidelines directed at infections with higher bacterial burden have historically recommended ASPs (6,7). Recently, a prospective observational study evaluated cefazolin for the presence of the inoculum effect (defined as an increase of MIC to ≥16 μg/mL when tested at 10^7 CFU/mL) (15). In 77 patients, 42 patients (54.5%) were positive for the inoculum effect, leading to an increased risk of 30-day mortality (risk ratio, 2.65; 95% CI: 1.1–6.42; P=0.03) (15).

Over 90% of *Staphylococcus aureus* strains produce a Bla, which hydrolyze penicillin (16). There have been four different types identified, A, B, C, and D (16). Type A Blas have demonstrated the most enhanced hydrolysis of cefazolin over ASPs with type C also maintaining some activity (16). Despite the limitations from the inoculum effect, cefazolin has many advantageous qualities compared to ASPs, as shown in *Table 1*. Regarding drug dosing, the

Table 1 Characteristics of cefazolin and antistaphylococcal penicillins

Characteristics	Cefazolin	Nafcillin/oxacillin
Advantages	Well-tolerated	Resistant to inoculum effect
	Can be used in patients experiencing immune-mediated hypersensitivity to nafcillin	Preferential for endocarditis and meningitis
	No drug interactions	No unnecessary Gram-negative exposure
	Lower cost	
Disadvantages	Subject to the inoculum effect	High rates of adverse events
	Hydrolyzed by type A and C beta-lactamases	High rates of discontinuation due to adverse events
	Minimal CNS penetration	Thrombophlebitis with continuous infusion
	Higher doses needed for obese patients	Frequent daily dosing (6×/day)
		Drug interactions
		Cytochrome p450 enzyme induction
Dosing	CrCl >35 mL/min: 2 grams every 8 hours	2 grams every 4 hours, no adjustment for renal dysfunction
	CrCl 10–34 mL/min: 1 gram every 12 hours	Dose reduction for combined renal and hepatic impairment
	CrCl <10 mL/min: 1 gram daily	
	HD: 2 grams after HD on Monday, Wednesday, and 3 grams after HD on Friday	

CNS, central nervous system; CrCl, creatinine clearance; HD, hemodialysis.

half-life of cefazolin in patients with normal renal function is approximately 2 hours, which supports every 8 hours dosing with adjustments for patients with reduced kidney function (16). Dosing in hemodialysis has been simplified to include only a 2–3 grams dose after each hemodialysis session (16). The recommended dose of nafcillin or oxacillin directed at severe or invasive infections is 2 grams every 4 hours with no dosing reductions necessary for renal impairment (16). Continuous infusion models have been developed to circumvent the multiple daily dosing but have been associated with thrombophlebitis and extravasation (16). In addition to its favorable dosing regimen, cefazolin is also associated with considerably fewer side-effects than ASPs. Individual rates of reactions vary between studies. One study reported significantly more adverse reactions with oxacillin than nafcillin (59% *vs.* 28%, respectively, P<0.001) with the most common adverse effects being neutropenia, hepatotoxicity, rash, phlebitis, and fever (17). Another study reported higher discontinuation rates with nafcillin than oxacillin (18% *vs.* 2%, respectively, P=0.0004) and higher rates of hypokalemia (51% *vs.* 17%, respectively, P<0.0001) (18). In contrast, the most common adverse effect for cefazolin includes a mild rash (16).

Consistent with previous reports, the study by Bidell and colleagues further demonstrated a reduction in treatment discontinuation due to adverse events with cefazolin as compared to ASPs (8). Cefazolin has consistently demonstrated that it is better tolerated than ASP, and the meta-analysis confirms this with an OR of 0.25 (95% CI: 0.11–0.56] (8). The continued debate and still unanswered question is whether cefazolin has equal efficacy compared to ASPs. This study found no difference in clinical failure (OR 0.85, 95% CI: 0.41–1.76) but noted a significant difference in 90-day mortality (OR 0.63, 95% CI: 0.41–0.99), favoring cefazolin (8). This finding is worthy of further exploration.

Taking a closer look at the included studies, 6 of the 7 are retrospective in design and 1 was a prospective observational cohort, see *Table 2* (2,19-24). These design limitations are subject to a selection bias in which sicker patients or patients with deeper seated infections may be preferentially started on the presumed superior agent. Looking specifically at the five studies that included a breakdown of patients with

Table 2 Review of literature comparing cefazolin to antistaphylococcal penicillins

Author/year	Design/patients	Number of patients with deep-seated infections	Clinical outcomes
Lee, 2011 (19)	Retrospective, case-control/cefazolin (n=49) *vs.* nafcillin (n=84)	Cefazolin: 1 (2%) with IE, 10 (20%) with OM; nafcillin: 13 (16%) with IE, 11 (13%) with OM	No significant difference in incidence of treatment failure
Paul, 2011 (20)	Retrospective cohort/cefazolin (n=72) *vs.* cloxacillin (n=281)	Not subgrouped by antibiotic, however 6.5% with IE and 15.3% with OM	No significant treatment differences between groups
Li, 2014 (21)	Retrospective cohort/cefazolin (n=59) *vs.* Oxacillin (n=34)	Cefazolin: 27 (18%) with IE, 18 (31%) with OM; oxacillin: 3 (9%) with IE, 20 (59%) with OM	No significant treatment differences between groups
Bai, 2015 (2)	Retrospective cohort/cefazolin (n=105) *vs.* cloxacillin (n=249)	Cefazolin: 2 (2%) with IE, 15 (14%) with OM; nafcillin: 30 (12%) with IE, 28 (11%) with OM	No difference in mortality between groups
Pollett, 2016 (22)	Retrospective cohort/cefazolin (n=70) *vs.* Nafcillin (n=30)	IE not identified as a source; for OM, 5 (7%) received cefazolin and 3 (10%) received nafcillin	Cefazolin associated with a nonsignificant reduction in mortality
McDanel, 2017 (23)	Retrospective cohort/cefazolin (n =1,163) *vs.* nafcillin/oxacillin (n=2,004)	Cefazolin: 52 (4%) with IE, 138 (12%) with OM; ASP: 145 (7%) with IE, 267 (13%) with OM	Cefazolin associated with a lower risk of 90-day mortality than ASPs
Lee, 2018 (24)	Prospective, observational cohort/ cefazolin (n=79) *vs.* nafcillin (n=163)	Cefazolin: 1 (1%) with IE, 28 (35%) with OM; nafcillin: 11 (7%) with IE, 61 (37%) with OM	Cefazolin was better-tolerated than nafcillin

IE, infectious endocarditis; OM, osteomyelitis; ASP, antistaphylococcal penicillin.

infective endocarditis, significant differences in the baseline characteristics emerge. Using a Fisher's exact test, patients treated with an ASP were statistically more likely to have endocarditis (8% *vs.* 5.7%, P=0.007). The included study by McDanel and colleagues, which accounted for over 70% of the patients and 71% of the ASP-related 90-day mortality events in the studies included in the meta-analysis, also noted the treatment differences in endocarditis patients (23). Available data to this point is only suggestive and ultimately calls for a prospective, randomized controlled trial focusing specifically on deeper seated infections with well-balanced intervention groups.

For patients initiated on nafcillin who develop a non-IgE-mediated hypersensitivity reaction, switching to cefazolin appears to be a safe and effective solution (24). Blumenthal and colleagues identified 60 patients from an outpatient parenteral antimicrobial therapy program who were switched to cefazolin during their course, with 17 patients experiencing a non-IgE-mediated reaction. All but 1 had resolution of the reaction and completed the full treatment course, and no patient developed any further complication (25). Another important consideration is the lack of central nervous system (CNS) penetration of cefazolin. As such, cefazolin should not be used for meningitis or other infections of the CNS; nafcillin or oxacillin are preferred (16).

Ultimately, for most non-CNS infections, cefazolin can be used preferentially to ASPs. In patients with slow-to-resolve or nonresolving infections a therapy change to an ASP should be considered. ASPs are preferred for meningitis given superior CNS penetration, and patients who are unable to tolerate an ASP can be treated with vancomycin and meropenem. For endocarditis, ASPs should still be considered preferentially until a large, randomized controlled trial focusing on high bacterial-burden infections is conducted with cefazolin being reserved for patients who are intolerant to ASPs (7). Finally, patients who cannot tolerate ASPs (excluding IgE-mediated reactions) can safely be switched to cefazolin. The utility of cefazolin for infections with lower bacterial burden is well-established; however, further studies are needed to define the optimal antimicrobial to treat MSSA infections with higher bacterial burden, such as infective endocarditis.

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Footnote

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