High prevalence of the cefazolin inoculum effect in methicillin-susceptible *Staphylococcus aureus* causing bloodstream infections in a hospital network in Houston, TX

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Introduction

Anti-staphylococcal penicillins (AsPen) or cefazolin are the drugs of choice for methicillin-susceptible *Staphylococcus aureus* (MSSA) bloodstream infections.[1] Nevertheless, in certain scenarios cefazolin's efficacy may be compromised by the cefazolin inoculum effect (CzIE), defined as an increase in the minimum inhibitory concentration (MIC) of cefazolin to ≥16mg/L when a high inoculum (≥5x10^7 CFU/ml) is present. Previous studies have suggested that the prevalence of the CzIE varies geographically, with high prevalence in some Latin American countries.

Observational studies from Argentina[2] and South Korea[3] have suggested the CzIE is associated with worse clinical outcomes in those treated with cefazolin. Prospective data evaluating the presence of the CzIE in deep-seated MSSA infections across the United States are lacking.

Methods

We performed a prospective observational study of MSSA bacteremia in a network of 13 hospitals in Houston, TX.

Inclusion criteria:

- ≥ 18 years old
- Positive blood culture with MSSA
- At least one follow-up blood culture, to determine microbiological outcomes
- Received cefazolin or nafcillin as definitive therapy (drug therapy for 72 hours or longer, and after culture results known)
- Original isolate available for evaluation of the CzIE

Exclusion criteria:

- Polymicrobial BSI
- Other antibiotics with MSSA activity in the definitive therapy period

Cefazolin MICs for all isolates were determined by broth microdilution at standard and high inoculum.

Results

50 patients were enrolled from 2/15/2020-4/30/2020

Table 1: Baseline characteristics

	Inoculum effect n=16	No Inoculum effect n=34	P value
Age	60.4	57.3	0.471
Male gender	11 (68.75)	24 (70.59)	1
Race			1
African American	3 (18.75)	7 (20.59)	
American Indian	0	1 (2.94)	
Caucasian	6 (37.50)	11 (32.35)	
Asian	1 (6.25)	1 (2.94)	
Other	4 (25)	9 (26.47)	
Unknown	2 (12.50)	5 (14.71)	
Ethnicity			0.882
Hispanic	4 (25)	11 (32.35)	
Charlson comorbidity index ≥ 5	10 (62.5)	13 (38.24)	0.136
On dialysis before admission	5 (25)	13 (38.24)	0.524
Immunocompromised	1 (6.25)	3 (8.82)	1
qSOFA ≥ 1	10 (62.5)	16 (47)	0.372
Jackson/McCabe			1
Non-fatal	14 (87.50)	28 (82.35)	
Ultimately fatal	2 (12.50)	6 (17.65)	
ICU admission	3 (18.75)	5 (14.71)	0.861
Source			0.546
Primary	3 (18.75)	14 (41.18)	
Secondary	13 (81.25)	20 (58.82)	
Sites of infection			0.486
Bone/joint	2 (12.5)	4 (11.76)	
CNS	0	2 (5.88)	
Endovascular	4 (25)	5 (14.71)	
Respiratory	2 (12.5)	0	
Skin and soft tissue	5 (31.25)	9 (26.47)	
Complicated bacteremia	6 (37.50)	21 (61.76)	0.136

- A total of 16/50 (32%) of the MSSA isolates exhibited the CzIE.
- A total of 37/50 (74%) patients received cefazolin as definitive therapy.
- Complicated bacteremia was seen in 27/50 (54%) patients. A lower proportion of isolates from complicated bacteremia exhibited the CzIE, though this difference did not reach statistical significance.
- Two patients in our cohort died: both of whose isolates exhibited the CzIE and received cefazolin as definitive therapy.

Conclusion

We report a high prevalence of the CzIE in MSSA BSIs in a major US urban hospital network. Further evaluation of the clinical implications of the CzIE is urgently needed.

References

1. McDanel JS, Roghmann MC, Perencevich EN, et al. Comparative Effectiveness of Cefazolin Versus Nafcillin or Oxacillin for Treatment of Methicillin-Susceptible Staphylococcus aureus Infections Complicated by Bacteremia: A Nationwide Cohort Study. Clin Infect Dis. 2017 Jul 1;65(1):100-106. doi: 10.1093/cid/cix287.
2. Miller WR, Seas C, Carvajal LP, et al. The Cefazolin Inoculum Effect Is Associated With Increased Mortality in Methicillin-Susceptible *Staphylococcus aureus* Bacteremia. Open Forum Infect Dis. 2018 May 23;5(6):ofy123.
3. Lee S, Song KH, Jung SI, et al. Comparative outcomes of cefazolin versus nafcillin for methicillin-susceptible Staphylococcus aureus bacteraemia: a prospective multicentre cohort study in Korea. Clin Microbiol Infect. 2018 Feb;24(2):152-158.