UWTASP
tele-antimicrobial stewardship program

February 9, 2021

*Staphylococcus aureus B*acteremia: Cefazolin vs Nafcillin

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Objectives

- Compare clinical key differences between cefazolin and nafcillin for MSSA bacteremia
- Analyze physiological basis for cefazolin inoculum effect
- Discuss clinical implication of cefazolin inoculum effect

MSSA = methicillin susceptible *Staphylococcus aureus*

Patient Case

CC: 57 year old man complaining of fever and chills.

PMH: HTN, DM2, IV drug use

Physical Exam: Antecubital sites notable for injection marks

VS: HR 72, RR 16, 38.3°C

Allergies: No known drug allergies

Hospital Course: Presented to ED complaining of fever and chills with HR 109 and febrile. ID was consulted on day 2 of hospitalization.

CC = chief complaint; PMH = past medical history; HTN = hypertension; DM2 = type 2 diabetes mellitus; PIV = peripheral IV; VS = vital signs; ED = emergency department; HR = heart rate; RR = respiratory rate; ID = infectious diseases

Patient Case

10/1
- BCx PIV #1 – MSSA (1/2 bottles)
- BCx PIV #2 – MSSA (2/2 bottles)

10/2
- TEE – pending

STAPHYLOCOCCUS AUREUS, COAGULASE POSITIVE

	Microtiter MIC Interp	Microtiter MIC Value (mcg/mL)
Cefazolin	S	
Ceftriaxone	-	<=8
Clindamycin	R	>2
Erythromycin	R	>4
Levofloxacin	S	<=0.25
Moxifloxacin	S	<=0.25
Oxacillin	S	<=0.25
Tetracycline	S	<=2
Trimeth_Sulfamethoxazole	S	<=2
Vancomycin	S	1

Antibiotics:

- Vancomycin dosed per pharmacy
- Cefepime 2 g every 8 hours

Can we deescalate to just vancomycin?

BCx = blood culture

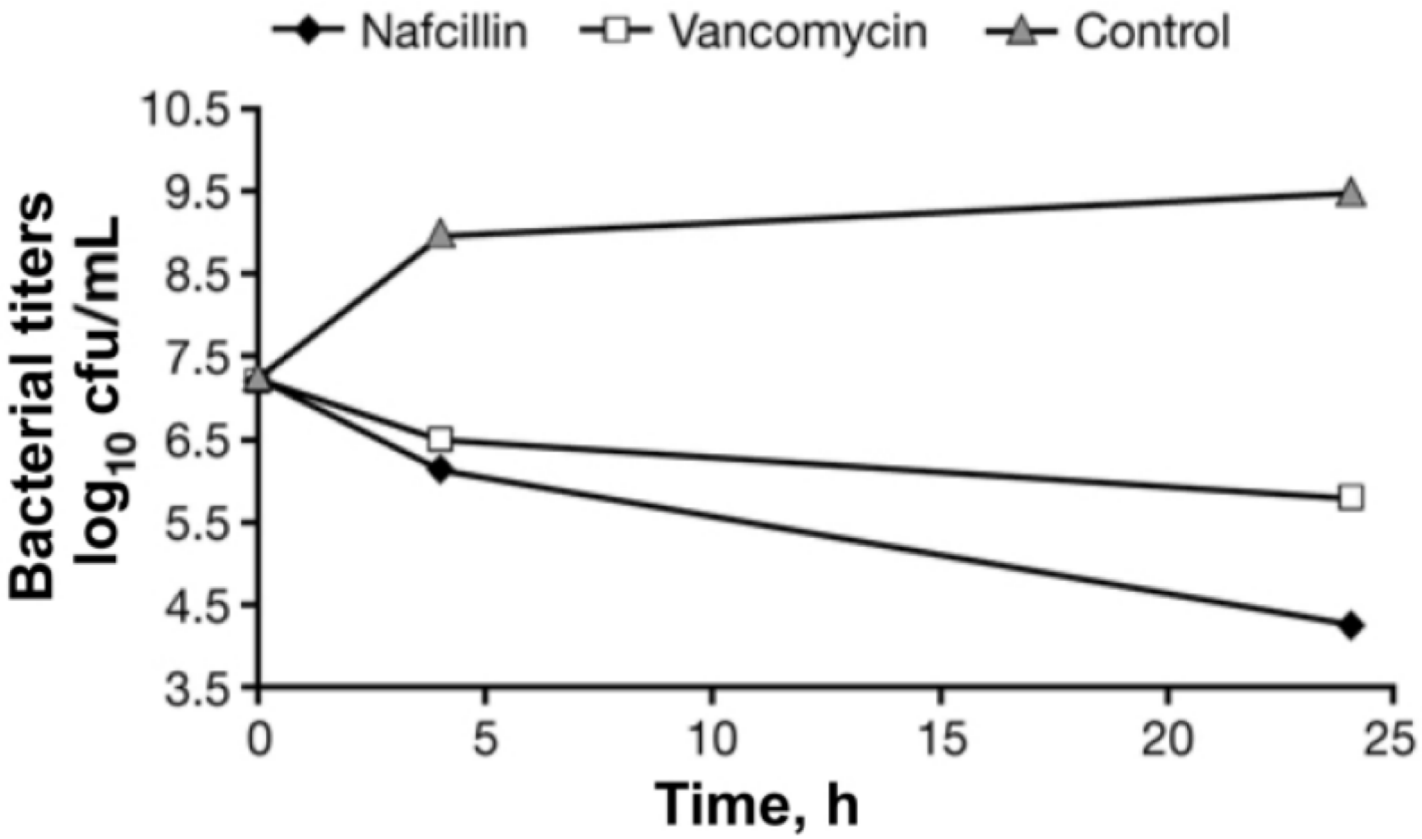
Complicated vs Uncomplicated *Staphylococcus aureus* Bacteremia

Uncomplicated - 14 days	Complicated – 28-42 days
• Intravascular catheter source removed within 5 days • Negative f/u blood culture 24-72 h after initial positive • Afebrile within 72 hours of initial positive culture • TTE/TEE without endocarditis • No metastatic infection • No indwelling intravascular prosthetic devices	• Positive f/u blood culture • Persistent fever • TTE/TEE with endocarditis • Metastatic infection

- Criteria helps choose correct duration systematically
- Complicated cases have higher relapse, morbidity, mortality if antibiotic course too short
- If course too long, patient at risk for ADEs and antibiotic overuse

Holland TL et al. *JAMA.* 2018;320(12):1249-1258.

Vancomycin vs Nafcillin



Time-kill curves for MSSA at 4x MIC

Stevens DL. Clinical Infectious Diseases 2006; 42:S51–7
Small PM and Chambers HF. *Antimicrob Agents Chemother*. 1990;34(6):1227-1231.

Vancomycin is Inferior for MSSA Bacteremia

- For MSSA bacteremia, vancomycin has been shown to have more…
  - Bacteremia for >7 days and relapse[1]
  - 14 day mortality and SAB related death[2]
- Increased mortality and relapse have been demonstrated in endocarditis as well[3,4]

[1]Chang FY et al. 2003 Sep;82(5):333-9
[2]Kim SH et al. Antimicrob Agents Chemother. 2008;52(1):192-197.
[3]Small PM and Chambers HF. Antimicrob Agents Chemother. 1990;34(6):1227-1231.
[4]Lodise TP et al. Antimicrob Agents Chemother. 2007 Oct; 51(10): 3731–3733.

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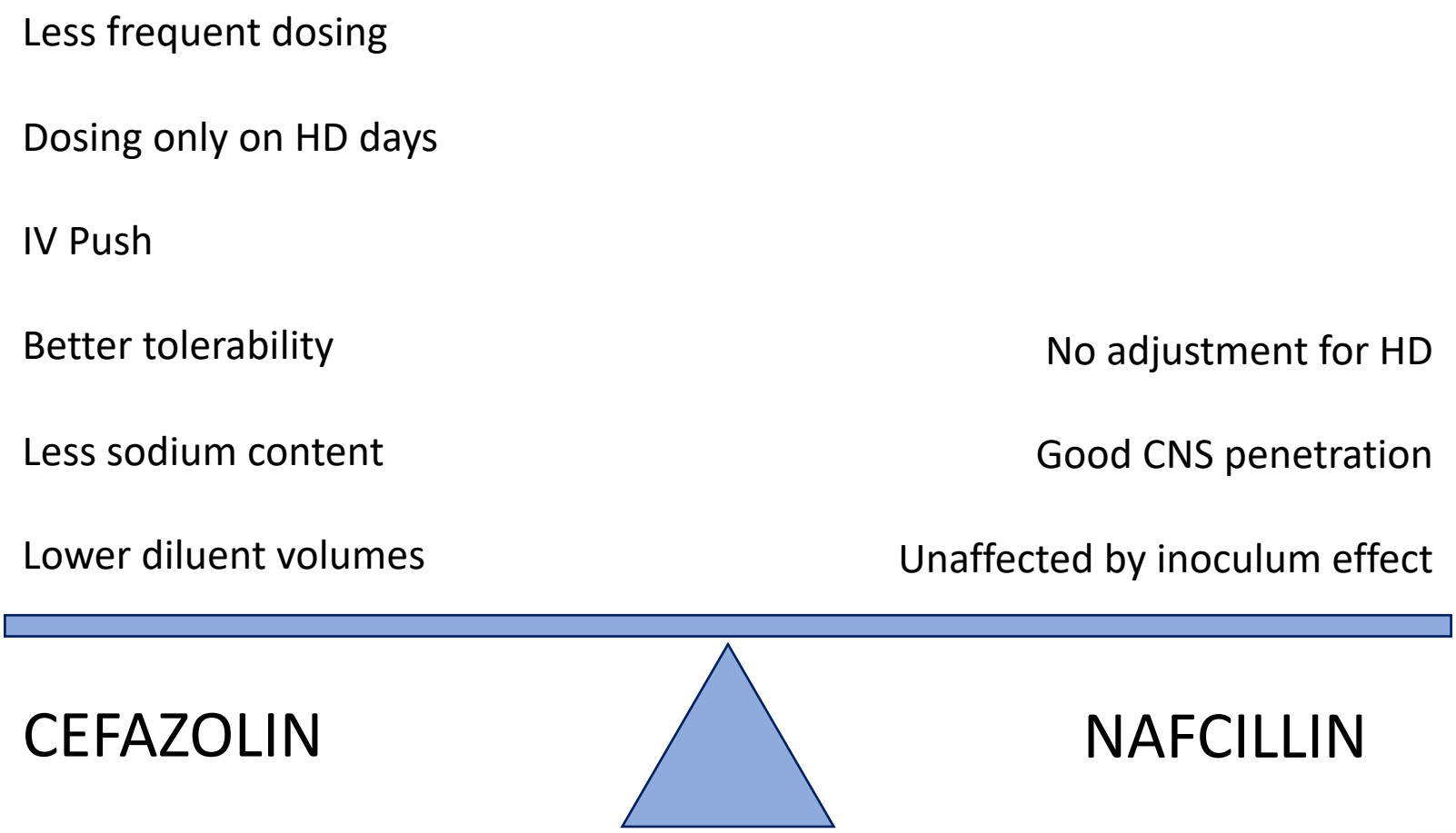
During ID rounds, a discussion ensues comparing nafcillin to cefazolin…

Can we de-escalate to just vancomycin?

BCx = blood culture

Why Cefazolin or Nafcillin?



Lexicomp Online, Pediatric and Neonatal Lexi-Drugs Online, Hudson, Ohio: UpToDate, Inc.; October 12, 2020

Cefazolin or Nafcillin for MSSA?

- No RCTs comparing nafcillin and cefazolin
- Meta-analyses[1,2] published based on retrospective data suggest that cefazolin tend to have
  - Less nephrotoxicity
  - Less hepatotoxicity
  - Less discontinuation due to ADR
  - Non-inferior mortality outcomes

What about inoculum effect?

[1]Allen JM et al. Infect Dis Ther. 2019 Dec;8(4):671-686.
[2]Eljaaly K, Alshehri S, Erstad BL. Antimicrobial Agents and Chemotherapy Mar 2018, 62 (4) e01816-17

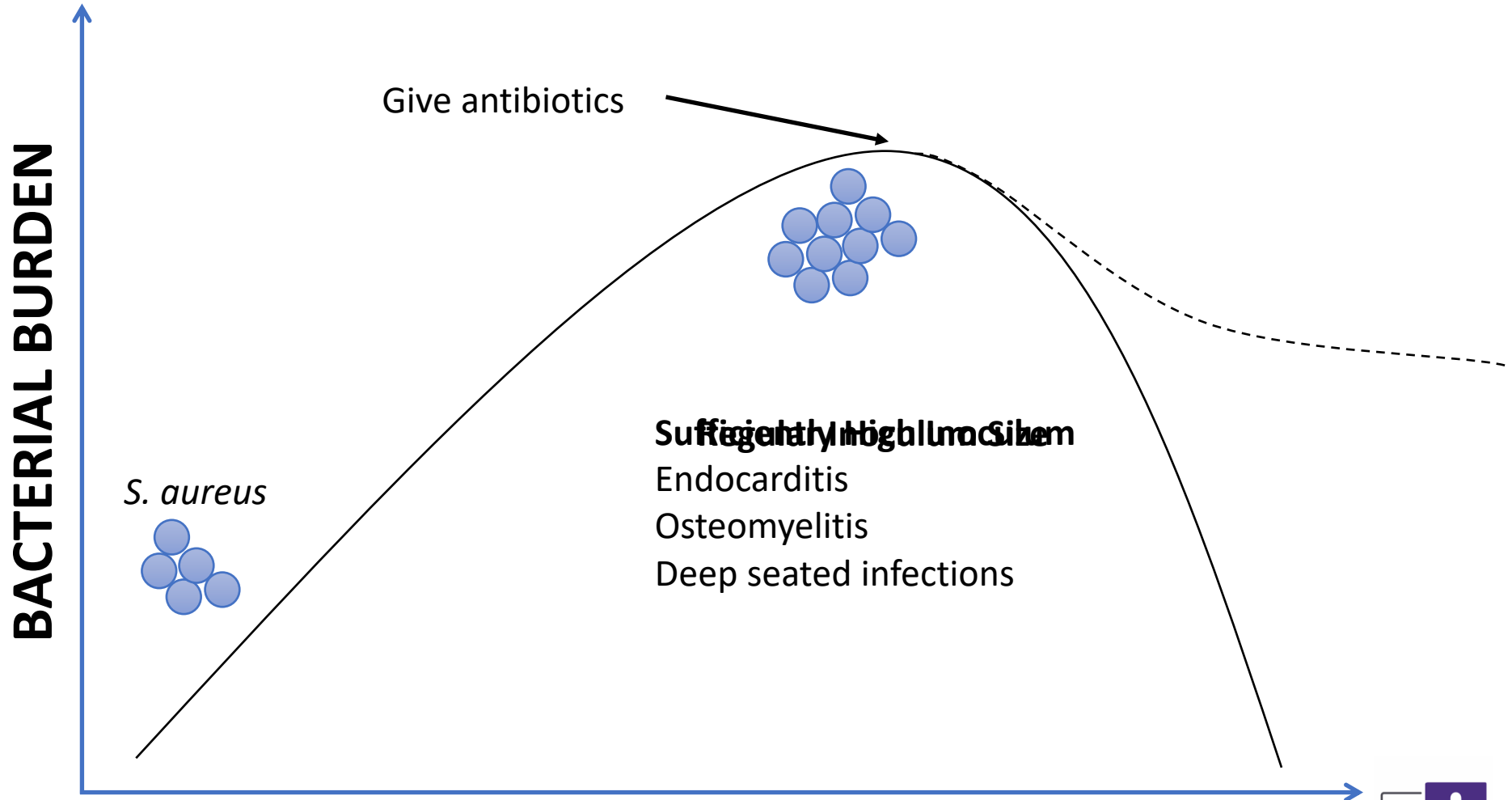
Clinical Concerns With Cefazolin

- Cefazolin inoculum effect (CIE) described *in vitro* and *in vivo* in high burden infections with MSSA as early as 1973
- Initial reports of failure were difficult to interpret has there may have been source control or site penetration issues
- CIE was not evaluated in the majority of case reports these case reports
- ASPs are not affected by inoculum effect from MSSA

Reller LB et al. Antimicrob Agents Chemother. 1973 Apr;3(4):488-97
Quinn EL et al. J Infect Dis. 1973 Oct;128:Suppl:S386-9
Li J et al. Pharmacotherapy. 2017 Mar;37(3):346-360

ASP = antistaphylococcal penicillin

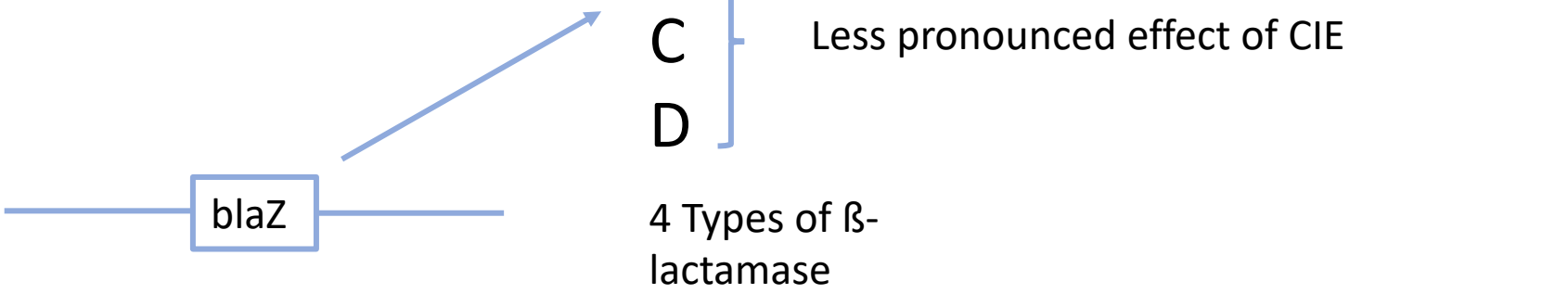
Inoculum Effect



Adapted from Kassamali Escobar, Z (2019). 'ID Week 2019 Highlights' [PowerPoint Presentation]. Available at https://www.uwtasp.org/content/idweek-2019-highlights (Accessed 30 January 2021)

Inoculum Effect: Gene

NOTE:
No standard testing for CIE and testing should not be done outside of research as recommended by CLSI



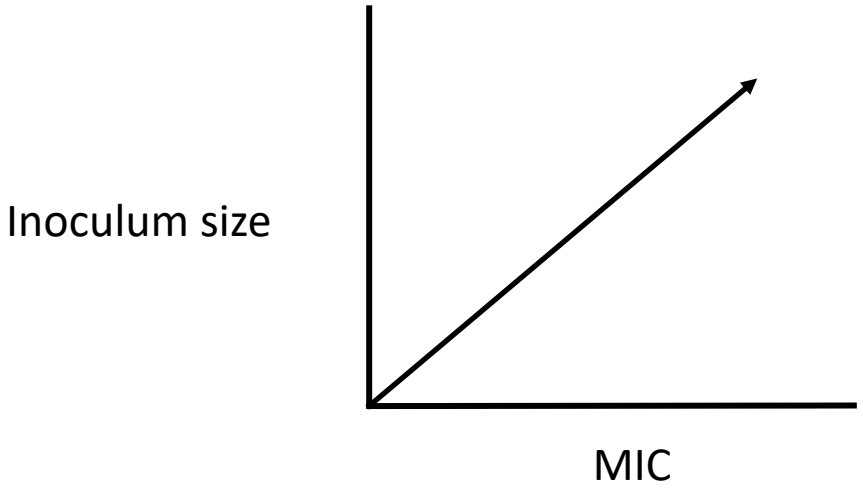
Gene for ß-lactamase found on MSSA

4 Types of ß-lactamase

Miller, William R, and Cesar A Arias. *The Cefazolin Inoculum Effect for MSSA*
Clinical & Laboratory Standards Institute, 2 Feb. 2019, clsi.org/about/blog/ast-news-update-2019-hot-topic/.

blaZ Impacts MICs

	blaZ Negative		blaZ Positive	
	Standard Inoculum	High Inoculum	Standard Inoculum	High Inoculum
Cefazolin MIC_{90}	≤0.5	≤0.5	≤0.5	4 (range ≤0.5-≥32)



100% of pronounced CIE were isotype A

Saeki M et al. J Infect Chemother. 2018 Mar;24(3):212-215

Laboratory Phenomenon?

- Static *in vitro* systems do not account for dynamic variables of *in vivo* systems

- Some experts consider it an artifact of susceptibility testing only

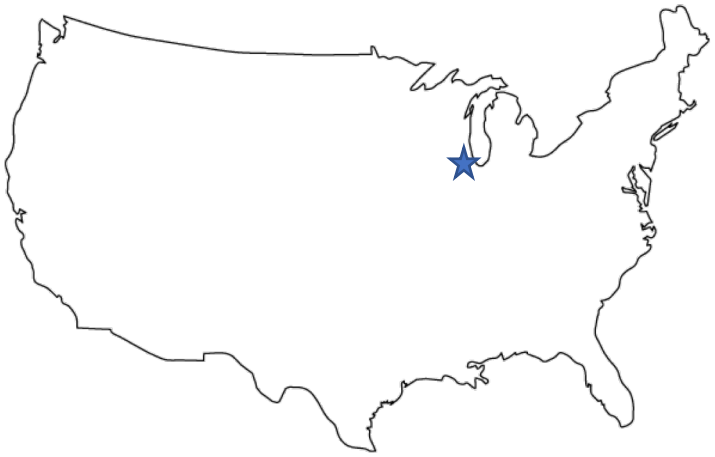
Craig WA, Bhavnani SM, et al. Diagnostic Microbiology and Infectious Disease, 50(4), 229–230

CIE a Geographical Phenomenon?

- Different geographical locations have different prevalence rates of pronounced CIE

Argentina 54.5%

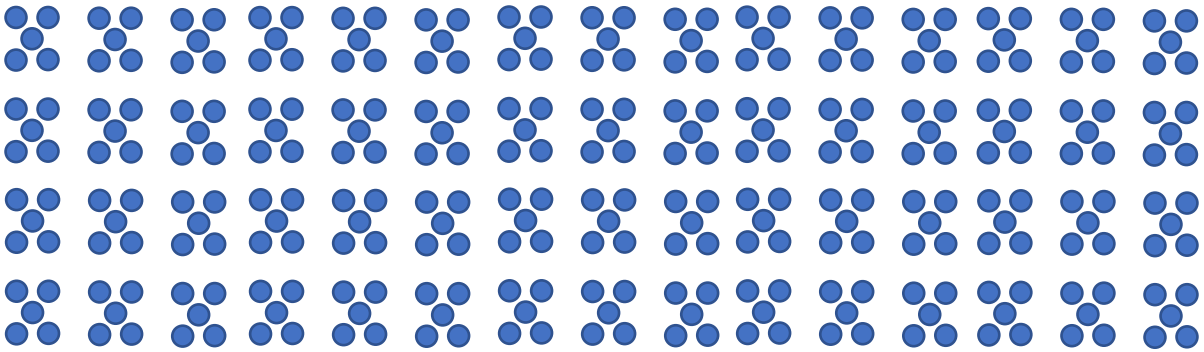
South Korea 13%



Chicago ???

Miller WR et al. Open Forum Infect Dis. 2018 May 23;5(6):ofy123
Chong YP et al. Eur J Clin Microbiol Infect Dis. 2015 Feb;34(2):349-55
Wang et al. Antimicrob Agents Chemother. 2018 Aug; 62(8): e00382-18.

Chicago MSSA Isolates



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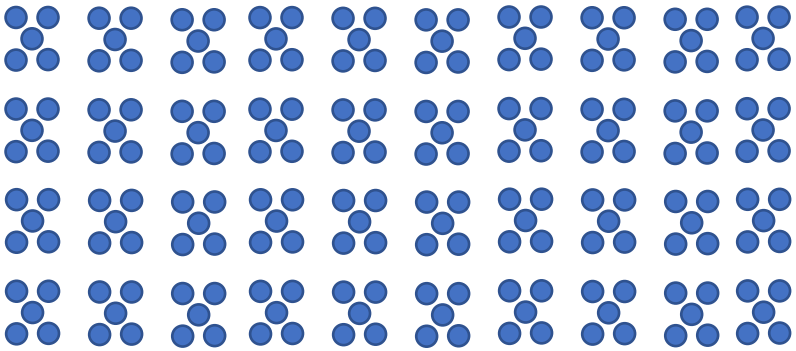

45	[illegible]	CIE

Wang et al. Antimicrob Agents Chemother. 2018 Aug; 62(8): e00382-18.

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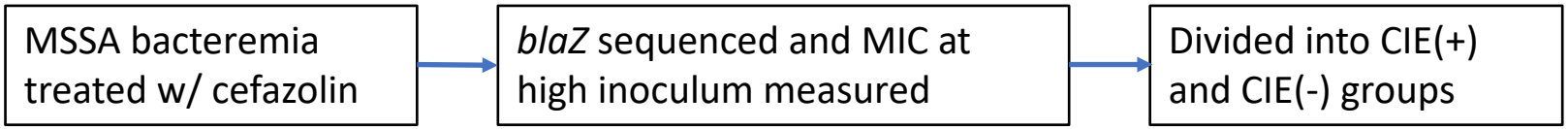
CIE and Clinical Implication

Study	Design

Lee et al., 2014 (Korea)	Retrospective cohort, n = 113
	
	<u>Outcomes at 12 weeks</u>:
	• Treatment failure (≥1 of the following)
	  • Switching antibiotics due to failure at clinician's discretion
	  • Recurrence of MSSA infection
	  • MSSA bacteremia associated mortality
	• Persistent bacteremia (≥72 h after initiation of cefazolin)

Study Design



Lee et al. Microb Drug Resist. 2014 Dec;20(6):568-74.

CIE and Clinical Implication

	CIE (+) N = 25	CIE(-) N = 20	P-value
	Stratified Analysis		
Persistent bacteremia > 72 h	16%	0	NC
Overall mortality	12%	0	0.46
Treatment failure	48%	25%	0.13

- Treatment failure and mortality were non-significantly different
- Persistent bacteremia was greater in CIE(+) group in the overall analysis
- Stratified analysis for high burden infections showed no significant difference

Lee et al. Microb Drug Resist. 2014 Dec;20(6):568-74.

Inoculum Effect Summary

- Inoculum effect only occurs in isolates with specific genes (most pronounced with type A)
- Not all high burden infections show inoculum effect
- Clinical failure has not been demonstrated consistently with cefazolin in high inoculum infections or CIE producing organisms
- CIE may be a geographic phenomenon
- CLSI does not recommend routine clinical lab testing for inoculum effect

Cefazolin vs Nafcillin Takeaway

Cefazolin tends to have…

- Less toxicity
- Less discontinuation due to ADR

Not all MSSA isolates will produce CIE

Likely a low number of isolates produce pronounce CIE in the US

Clinical implications of inoculum effect are still uncertain

Patient Case

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Current regimen:

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What do you recommend for antibiotic therapy?

Future Study

BMJ Open

Efficacy of cloxacillin versus cefazolin for methicillin-susceptible *Staphylococcus aureus* bacteraemia (CloCeBa): study protocol for a randomised, controlled, non-inferiority trial

Charles Burdet,[1,2] Paul Loubet,[1,3] Vincent Le Moing,[4] William Vindrios,[3] Marina Esposito-Farèse,[5,6] Morgane Linard,[2] Tristan Ferry,[7] Laurent Massias,[1,8] Pierre Tattevin,[9] Michel Wolff,[1,10] François Vandenesch,[11] Nathalie Grall,[1,12] Caroline Quintin,[5] France Mentré,[1,2] Xavier Duval,[1,6] François-Xavier Lescure,[1,3] for the CloCeBa study group

- First RCT comparing cefazolin and ASP for MSSA bacteremia
- Primary outcome: survival, relapse, and clinical success at day 90
- Study is still recruiting as of 2020
- Estimated completion date June 2022

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