Staph Meeting: A Case-Based Approach to Navigating Treatment of MSSA Bacteremia

A presentation for HealthTrust Members
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Pharmacist/Nurse Objectives

1. Recall the efficacy and safety of cefazolin versus anti-staphylococcal penicillins, other cephalosporins, and vancomycin
2. Recognize the clinical relevance of the inoculum effect when selecting beta-lactam therapy for Methicillin-Susceptible Staphylococcus Aureus (MSSA)
3. Identify evidence-based guidelines for de-escalation from vancomycin or broad-spectrum cephalosporins, such as cefepime and ceftriaxone, to cefazolin in confirmed MSSA infections

Pharmacy Technician Objectives

1. Identify pros and cons with cefazolin when treating Methicillin-Susceptible Staphylococcus Aureus (MSSA) infections
2. Recall dosing frequencies between cefazolin and ceftriaxone
3. Recognize common preparation details with cefazolin

Abbreviations

- **ABX:** antibiotic
- **ADE:** adverse drug event
- **APBL:** antipseudomonal beta-lactam
- **ASP**: anti-staphylococcal penicillin
- **AKI**: acute kidney injury
- **AIN**: acute interstitial nephritis
- **AUC**: area under the curve
- **BSI**: bloodstream infection
- **CSF**: cerebrospinal fluid
- **CzIE**: cefazolin inoculum effect
- **ESBL**: extended-spectrum beta lactamase
- **GI**: gastrointestinal
- **GNR**: gram negative rods
- **ICU**: intensive care unit
- **IDSA**: Infectious Diseases Society of America
- **LOS**: length of stay
- **MRSA**: methicillin-resistant *staphylococcus aureus*
- **MSSA**: methicillin-susceptible *staphylococcus aureus*
- **OPAT**: outpatient antibiotic therapy
- **PCN**: penicillin
- **PBP**: penicillin-binding protein
- **SOC**: standard of care
- **RRT**: renal replacement therapy
- **VRE**: vancomycin resistant enterococci

Background

Staphylococcus aureus: Virulence & Host Interaction

Gram-positive cocci in clusters, typically found in human nares, skin, throat, and GI tract

Virulent pathogen in the presence of skin or mucosal breaches leading to entrance to the bloodstream

Virulence factors: cell wall-anchored proteins which covalently attach to peptidoglycan

- Adhesion and invasion of host cells
- Evasion of immune responses
- Biofilm formation

Sources: Tong SYC, et al. JAMA. 2025;334(9):798-808
Foster TJ, et al. Nat Rev Microbiol. 2014;12(1):49-62

Global Burden & Outcomes of *Staphylococcus aureus* bacteremia

Deaths Per Year Worldwide

~300,000

Leading Cause of Mortality

90-day mortality: ~30%

30-Day Readmission Rate

22%

Sources: Tong SYC, et al. *JAMA*. 2025;334(9):798-808
Bai AD, et al. Clin Microbiol Infect. 2022;28(8):1076-1084
Kengo I, et al. *Clin Infect Dis*. 2019;69(12):2112-2118

S. aureus bacteremia: Classification & Diagnosis

Uncomplicated

- Presence of persistent bacteremia (positive follow-up blood cultures > 48 -72h)
- Evidence of metastatic infection

Complicated

Methicillin-resistant (MRSA) vs. methicillin-susceptible (MSSA)
- Based on antibiotic susceptibility and presence of mecA gene -

Must quickly rule out Endocarditis:
Transthoracic echocardiography (TTE) suggested in patients with S. aureus bacteremia
Patients with high risk for endocarditis should undergo transesophagealechocardiography (TEE)

Sources: Tong SYC, et al. *JAMA*. 2025;334(9):798-808
Liu C, et al. *Infect Dis Society of America*. 2011;52(3):e18-55.
Kaasch AJ, et al. Clin Infect Dis. 2011;53(1):1-9.

MSSA Bacteremia: Common Sites of Metastatic Infection

- Infective endocarditis
- Bone/joint infections (BJI) (i.e. osteomyelitis, prosthetic joint infections)
- Severe skin/soft tissue infections (i.e. catheter-related, abscesses)

Sources: Tong SYC, et al. *JAMA*. 2025;334(9):798-808
Fowler VG Jr, et al. Arch Intern Med. 2003;163(17):2066-72

MSSA Bacteremia: Risk Factors

Presence of implanted devices: central venous catheters, implanted cardiac or other prosthetic devices
IV drug use
Chronic hemodialysis
Immunocompromised status: HIV/AIDS, immunosuppressive therapy (corticosteroids)
Recent surgery
History of S. aureus colonization or infection

Sources: Tong SYC, et al. *JAMA*. 2025;334(9):798-808
Souli M, et al. Clin Infect Dis. 2019;69(11):1868-1877

Current Guideline Recommendations for MSSA bacteremia

American Family Physician – 2005

- 1st-line: anti-staphylococcal penicillins
- Alternative: cefazolin
- Vancomycin should be used in patients with PCN allergy

Infectious Disease Society of America (IDSA) – 2011

- Beta-lactam antibiotics are the drugs of choice in absence of allergy

Sources: Liu C, et al. *Infect Dis Society of America*. 2011;52(3):e18-55.
Bamberger DM, et al. *Am Fam Physician*. 2005;72(12):2474-2481.

Inoculum Effect: Questionable Efficacy in Cefazolin Use

Low Bacterial Counts

MIC ≤ 8

MSSA Susceptible to Cefazolin

High Bacterial Counts

MIC ≥ 16

MSSA Resistant to Cefazolin

Routine cefazolin susceptibility does **not** detect inoculum effect

Mediated by BlaZ Enzyme (Beta Lactamase)

Sources: Lo CK, et al. *JAC-antimicrobial resistance*. 2024;6(3):dlae069
Nannini EC et al. *Antimicrobial agents and chemotherapy*. 2009;53(8):3437-41

When is the Inoculum Effect Most Concerning?

Endocarditis

Vegetations harbor large bacterial burden

Osteomyelitis & Septic Arthritis

Deep-seated infections with poor drug penetration and high bacterial burden

Severe Pneumonia

Specifically, in Ventilator-associated or necrotizing presentations

Sources: Lo CK, et al. *JAC-antimicrobial resistance*. 2024;6(3):dlae069
Nannini EC et al. *Antimicrobial agents and chemotherapy*. 2009;53(8):3437-41

Effect of Cefazolin Inoculum Effect (CzIE) on Treatment Outcomes

Lo KF Calvin, et al

Systematic Review
- Serious MSSA infections
- Treated with cefazolin
- Do MSSA isolates that show CzIE result in worse clinical outcomes than infection due to MSSA isolates without CzIE?

Evaluated 23 studies:
- None found significant difference in mortality
- All but one found no significant difference in treatment failure

Key Takeaways: While CzIE is significant in the lab, no attributable difference in mortality was noted when choosing between agents

Source Control is key

Sources: Lo CK, et al. *JAC-antimicrobial resistance*. 2024;6(3):dlae069
Nannini EC et al. *Antimicrobial agents and chemotherapy*. 2009;53(8):3437-41

Review of Recommended Treatments in MSSA Bacteremia

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Recommended Treatments

Anti-staphylococcal Penicillin

- Nafcillin, oxacillin
- Historically recommended to MSSA bacteremia
- Associated with increased risk of adverse events
  - Interstitial nephritis
  - Injection site reactions
  - Hepatotoxicity, increased transaminases
- Pharmacokinetics
  - Wide distribution; poor CSF penetration
  - Short half-life; frequent dosing (Q4h)
- Preparation: compatible with dextrose 5% in water (D5W)

Cefazolin

- 1st generation cephalosporin
- Can be used in cases of PCN allergy
- Generally well tolerated
  - Lower incidence of AKI compared with ASPs (13% vs. 32%, $p = 0.007$)
- Pharmacokinetics
  - Wide distribution; low CSF penetration
  - Moderate half-life; Q8h dosing frequency
- Preparation:
  - Compatible with D5W and 0.9% normal saline (NS)
  - Commonly prepared with NS

Source: Flynt LK et al. Infect Dis Ther. 2017;6(2):225-231.

Beta-Lactam Cross Reactivity

β-Lactam Allergy Listed

	Penicillins					1st		2nd			3rd			4th	5th			Carbapenem		Mono	Classes		
	Penicillin	Ampicillin	Amoxicillin	Nafcillin	Piperacillin	Cephalexin	Cefazolin	Cefaclor	Cefoxitin	Cefuroxime	Ceftriaxone	Cefdinir	Ceftazidime	Cefepime	Ceftaroline	Ceftolozane	Cefiderocol	Ertapenem	Meropenem	Aztreonam	For non-specific allergies, collect specifics of allergy (i.e. drug, severity, timing)	"Penicillins"	"Cephalosporins"
Penicillin		N	N	CP	CP	N	Y	UA	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		N*	CP*
Ampicillin	N		N	CP	CP	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		N*	CP*
Amoxicillin	N	N		CP	CP	N	Y	N	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		N*	CP*
Nafcillin	CP	CP	CP		CP	CP	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		CP*	Y
Piperacillin	CP	N	CP	CP		N	Y	N	Y	Y	Y	Y	Y	Y	Y	Nc	Y	Y	Y	Y		N*	UA*
Cephalexin	N	N	N	CP	CP		Y	N	Y	Y	UA	Y	UA	Y	Y	Y	Y	Y	Y	Y		N*	N*
Cefazolin	Y	Y	Y	Y	Y	Y		Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		Y	N*
Cefaclor	UA	N	N	Y	CP	N	Y		Y	UA	UA	Y	Y	Y	Y	Y	Y	Y	Y	Y		N*	N*
Cefoxitin	N	Y	Y	Y	Y	Y	Y	Y		N	UA	Y	Y	Y	Y	Y	Y	Y	Y	Y		UA*	N*
Cefuroxime	Y	Y	Y	Y	Y	Y	Y	UA	N		N	Y	UA	N	UA	UA	CP	Y	Y	Y		Y	N*
Ceftriaxone	Y	Y	Y	Y	Y	UA	Y	UA	UA	N		UA	N	N	UA	UA	CP	Y	Y	CP		Y	N*
Cefdinir	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	UA		UA	UA	UA	UA	CP	Y	Y	Y		Y	N*
Ceftazidime	Y	Y	Y	Y	Y	UA	Y	Y	Y	UA	N	UA		N	UA	N	N	Y	Y	N		Y	N*
Cefepime	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	N	UA	CP		UA	CP	N	Y	Y	CP		Y	N*
Ceftaroline	Y	Y	Y	Y	Y	Y	Y	Y	Y	UA	UA	UA	UA	UA		N	CP	Y	Y	CP		Y	N*
Ceftolozane	Y	Y	Y	Y	Nc	Y	Y	Y	Y	UA	UA	UA	N	CP	UA		N	Y	Y	CP		Y	N*
Cefiderocol	Y	Y	Y	Y	Y	Y	Y	Y	Y	CP	CP	CP	N	CP	CP	CP		Y	Y	N		Y	CP*
Ertapenem	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y		CP	Y		Y	Y
Meropenem	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	CP		Y		Y	Y
Aztreonam	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	N	Y	Y	CP	N	Y	Y			Y	Y

*If non-specific allergies are reported (i.e. "penicillins") attempt to clarify the specifics of the allergy (i.e. drug, type/severity of reaction, timing, when reaction occurred, if treatment of allergic reaction was required, and if any other beta-lactams have been tolerated). Contact ID/pharmacy if further guidance is needed.

Y The order may be ordered/verified as long as any reaction other than type I-IV hypersensitivity reactions (HSRs). This includes general or non-specific allergy listings. For type I HSRs, **a beta-lactam with a different side chain CAN be safely administered**; however, prescribers should be notified to communicate this information and confirm the order. Avoid use in type II-IV HSRs.

UA "OK Unless Anaphylaxis" Agent may have limited or conflicting data or share a similar side chain. Order/verify as long as the reaction is NOT listed as a type I-IV HSR.

N Should not be ordered/verified due to a higher likelihood of cross-reactivity. If ordered, the prescriber should be notified, and a different agent considered.

- Nc = Extrapolation of beta-lactamase inhibitor

CP "Call Prescriber/Pharmacist" The agent may have limited or conflicting data or share a similar side chain. Risk/benefit should be evaluated.

Source: Collins CD et al. Clin Infect Dis. 2021;72(8):1404-1412.

	Penicillins					1st		
	Penicillin	Ampicillin	Amoxicillin	Nafcillin	Piperacillin	Cephalexin	Cefazolin	Cefaclor
Penicillin		N	N	CP	CP	N	Y	UA
Ampicillin	N		N	CP	CP	N	Y	N
Amoxicillin	N	N		CP	CP	N	Y	N
Nafcillin	CP	CP	CP		CP	CP	Y	Y
Piperacillin	CP	N	CP	CP		N	Y	N
Cephalexin	N	N	N	CP	CP		Y	N
Cefazolin	Y	Y	Y	Y	Y	Y		Y
Cefaclor	UA	N	N	Y	CP	N	Y	
Cefoxitin	N	Y	Y	Y	Y	Y	Y	Y
Cefuroxime	Y	Y	Y	Y	Y	Y	Y	UA
Ceftriaxone	Y	Y	Y	Y	Y	UA	Y	UA
Cefdinir	Y	Y	Y	Y	Y	Y	Y	Y
Ceftazidime	Y	Y	Y	Y	Y	UA	Y	Y
Cefepime	Y	Y	Y	Y	Y	Y	Y	Y
Ceftaroline	Y	Y	Y	Y	Y	Y	Y	Y
Ceftolozane	Y	Y	Y	Y	Nc	Y	Y	Y
Cefiderocol	Y	Y	Y	Y	Y	Y	Y	Y
Ertapenem	Y	Y	Y	Y	Y	Y	Y	Y
Meropenem	Y	Y	Y	Y	Y	Y	Y	Y
Aztreonam	Y	Y	Y	Y	Y	Y	Y	Y

Bottom line:
Cefazolin is safe to use in patients with PCN allergy. Cross-reactivity is low between these agents

Source: Collins CD et al. Clin Infect Dis. 2021;72(8):1404-1412.

Cefazolin vs. ASPs Meta-Analysis: Prosty, et al (2025)

Design:

- Meta-analysis of 30 observational studies
- Cefazolin (n=3869) vs.. ASPs (n=11644)
- Studies assessed from 2011 – 2024

Results:

- Primary outcome (30-day all-cause mortality): Cefazolin 8.6% vs.. ASPs 11.9%, 95% CI: 0.62 – 0.85
- Safety outcomes:
  - Treatment related adverse events more prevalent with use of ASPs
  - Lower toxicity within cefazolin group

Key Finding: Cefazolin use is better tolerated and associated with reduced mortality compared with ASPs

Source: Prosty C et al. Clin Microbiol Infect. 2025;31(8):1272-1282.

Cefazolin vs. ASPs: McDanel et al. (2017)

Design:

- N = 3167; Retrospective cohort, multicenter study (acute care VA hospitals)
- Cefazolin (n=1163) vs.. Nafcillin or Oxacillin (n=2004)
- Population: patients receiving cefazolin, nafcillin , or oxacillin for definitive treatment of MSSA; ~80% of both groups received empiric vancomycin
  - SSTI present in ~25%, osteomyelitis ~15%, endocarditis in <10% of patients

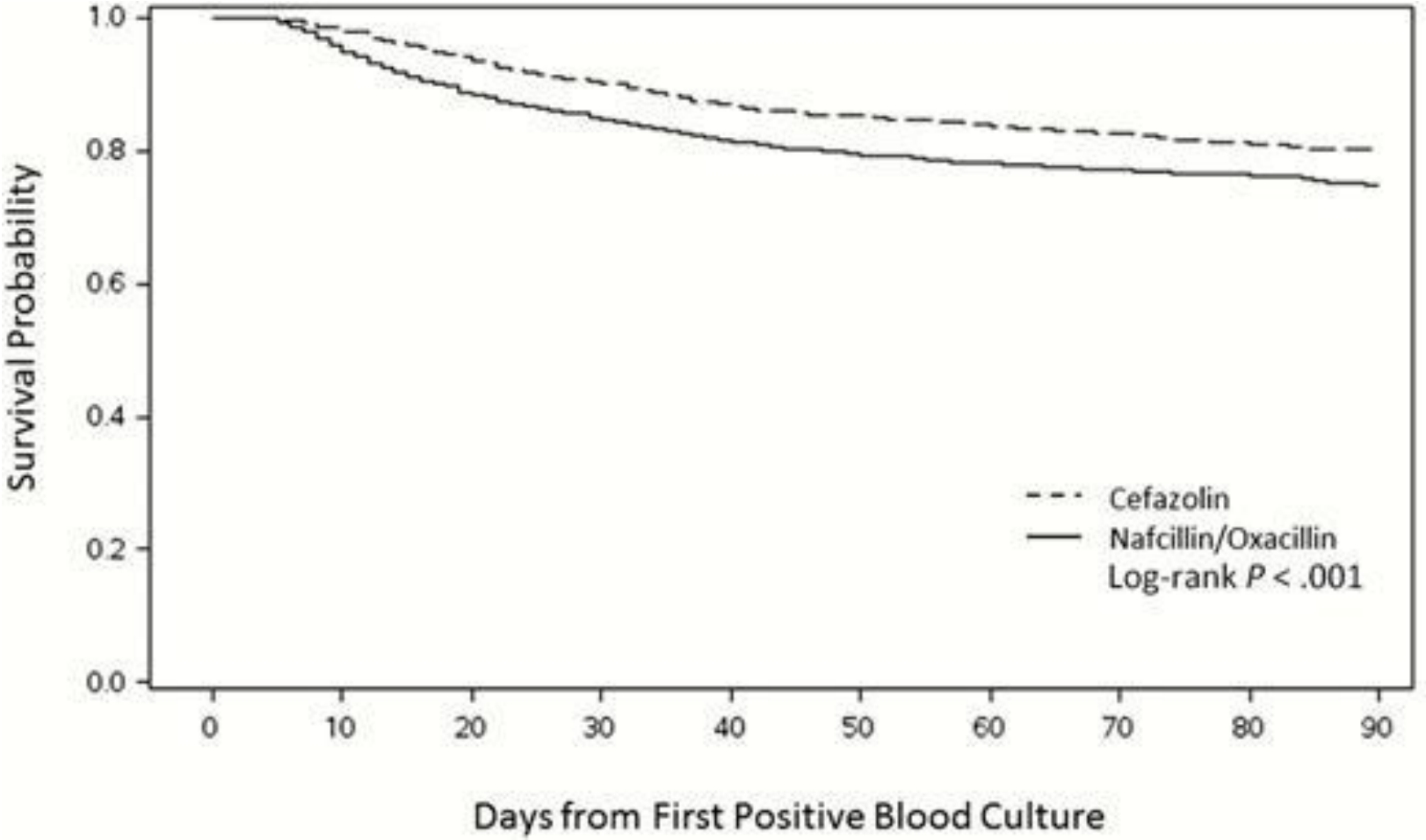
Results:

- Primary outcome (90-day all-cause mortality): Cefazolin 20% vs.. ASPs 25%, *P* = 0.001
- 90-day all-cause mortality defined as: death occurring within 90 days after the collection of the first positive MSSA blood culture

Key Finding: Cefazolin use for MSSA bacteremia can be associated with a lower risk of mortality compared with ASPs.

Source: McDanel JS et al. Clin Infect Dis. 2017;65(1):100-106.

Cefazolin vs. ASPs: McDanel, et al. (2017) – Outcomes



Source: McDanel JS et al. Clin Infect Dis. 2017;65(1):100-106.

Cefazolin vs. Nafcillin: Flynt et al. (2017)

Design:

- N = 149; Retrospective cohort, multicenter study (4-hospital health system in Detroit, MI)
- Cefazolin (n=68) vs.. Nafcillin (n=81)
- Population: patients receiving cefazolin or nafcillin ≥ 72h with at least one positive MSSA blood culture
  - BJI, endocarditis, and SSTI were most prevalently co-occurring in this patient population, 22% each
- Study period: November 2013 – October 2015

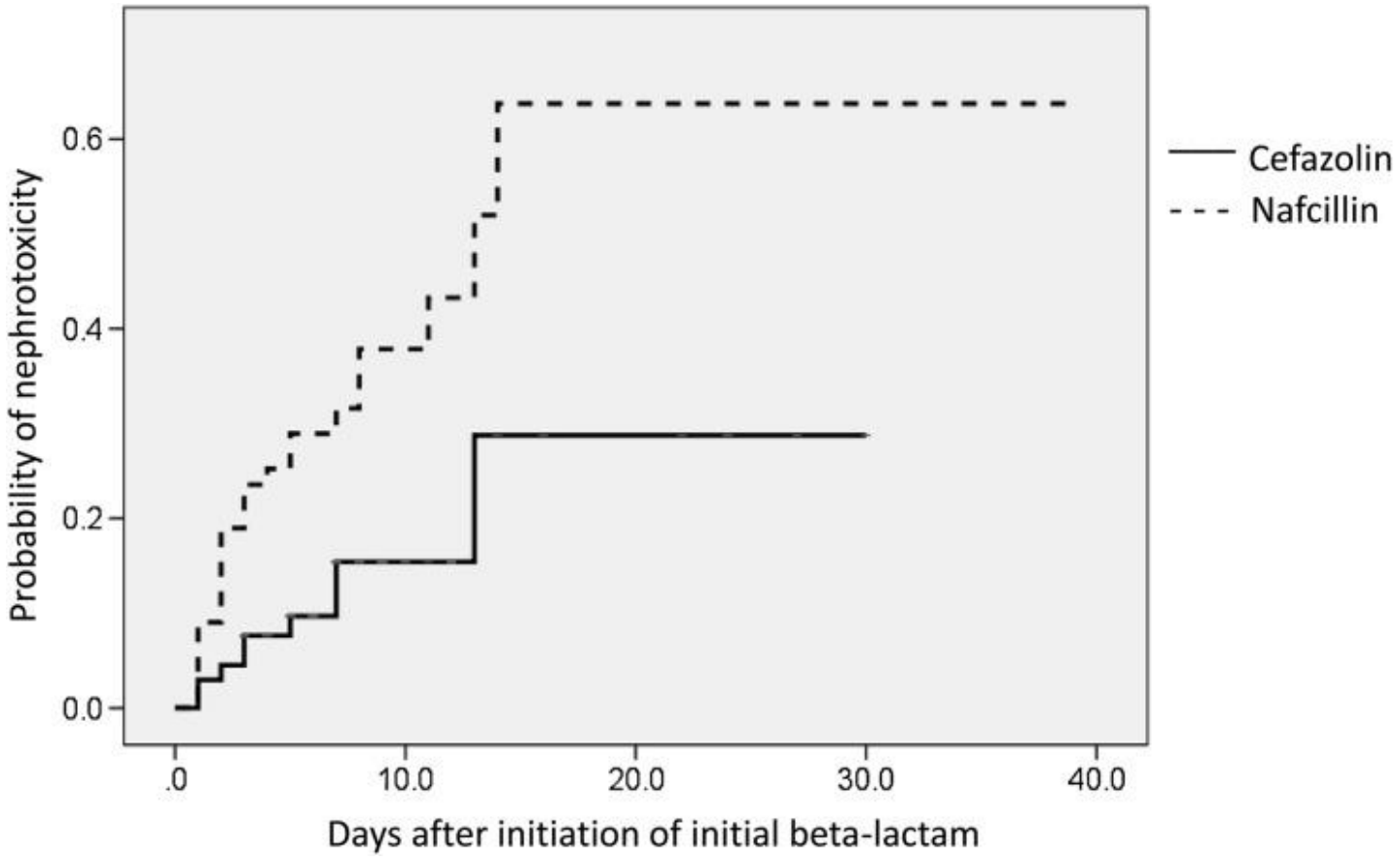
Results:

- Primary outcome (incidence of AKI): Cefazolin 13% vs.. Nafcillin 32%, *P* = 0.007
- AKI defined as: increase in SCr from baseline ≥ 0.3 mg/dL within 48h or any 50% increase from baseline

Key Finding: Nafcillin led to significantly more nephrotoxicity in the treatment of MSSA infections

Source: Flynt LK et al. Infect Dis Ther. 2017;6(2):225-231.

Cefazolin vs. Nafcillin: Flynt, et al. (2017) - Outcomes



Source: Flynt LK et al. Infect Dis Ther. 2017;6(2):225-231.

Cefazolin vs. Nafcillin: Miller, et al. (2020)

Design:

- N = 130; single-center retrospective study (467-bed tertiary academic medical center)
- Cefazolin (n=51) vs.. nafcillin (n=79)
- Population: patients receiving cefazolin **or** nafcillin ≥ 24h with MSSA-positive blood culture
  - Infectious source: Musculoskeletal (26.2%), endocarditis (16.9%), line-associated (13.8%), vascular (13.8%)
  - Source control: 52%
  - High inoculum infection: cefazolin 55% vs. nafcillin 59.5%
- Study period: October 2011 – December 2013

Results:

- Primary outcome (incidence of renal toxicity): nafcillin 25.3% vs.. cefazolin 2%, $p < 0.001$
  - Renal toxicity defined as serum creatinine ≥ 1.5x or 0.5 mg/dL from baseline
- No difference in clinical success and resolution of signs and symptoms

Key Finding: Cefazolin found to be better tolerated with lower risk of renal toxicity than nafcillin

Source: Miller MA, et al. J Microbiol Immunol Infect. 2020;53(2):321-327

Cefazolin vs. ASPs: Lefèvre, et al. (2021)

Design:

- N = 73; Quasi-experimental before-and-after ASP shortage, single-center cohort study (Nancy, France)
- Cefazolin (n=38) vs.. ASPs (n=35)
- Population: patients receiving cefazolin **or** ASPs with definite MSSA-positive infective endocarditis
- Study period: January 2015 – December 2018

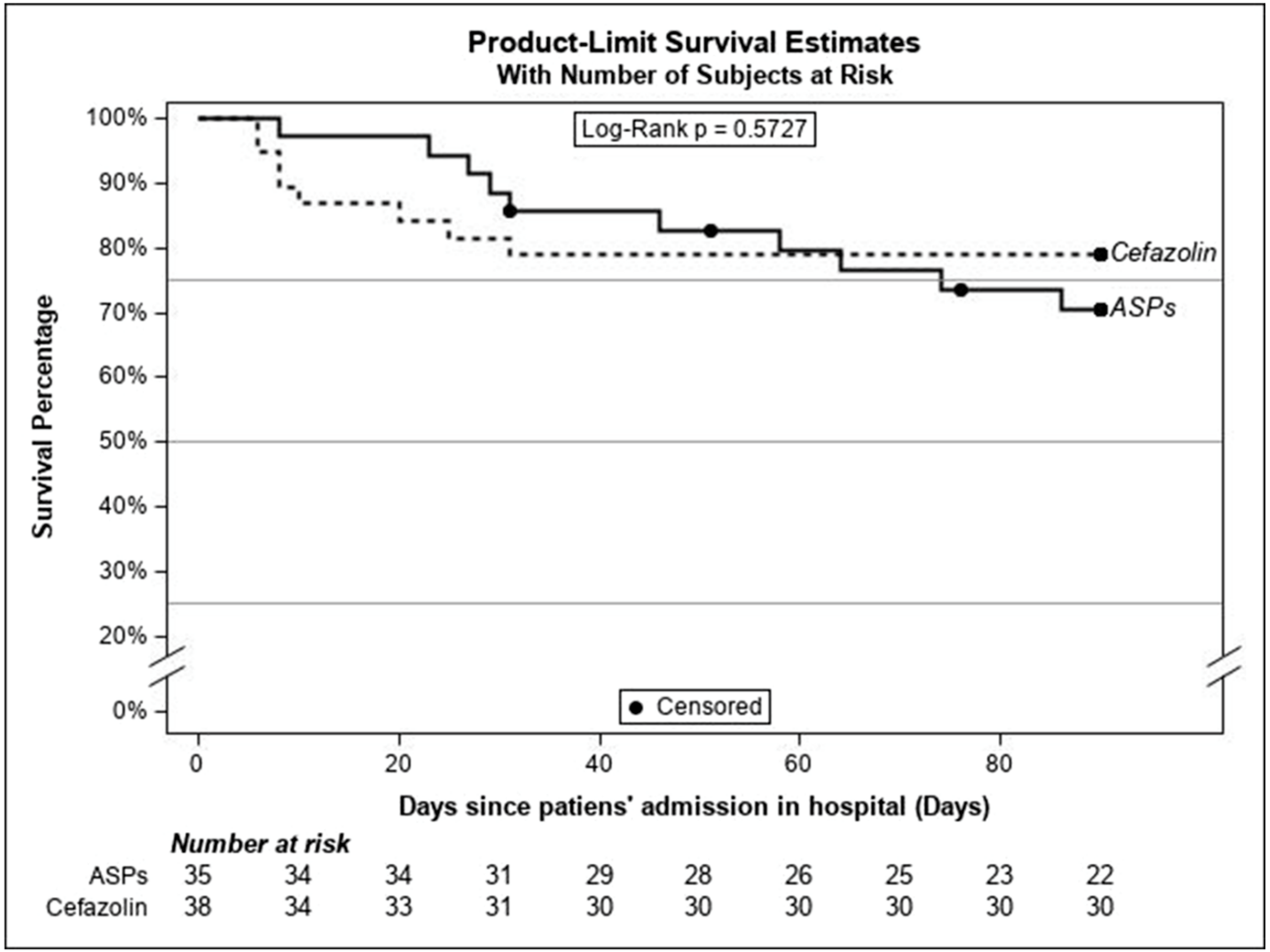
Results:

- Primary outcome (90-day mortality): ASPs 28.6% vs.. Cefazolin 21.1%, $p = 0.5727$
- No difference between groups for renal toxicity: 45.7% vs. 44.7%, $p = 0.933$

Key Finding: No difference in safety or efficacy between ASPs and cefazolin in the treatment of MSSA-positive infective endocarditis

Source: Lefèvre B, et al. Eur J Clin Microbiol Infect Dis. 2021;40(12):2605-2616

Cefazolin vs. ASPs: Lefèvre, et al. (2021) – Outcomes



Source: Lefèvre B, et al. Eur J Clin Microbiol Infect Dis. 2021;40(12):2605-2616

Patient Case 1

58 yo M with poorly controlled T2DM, MVR (Jul 2025), HTN, and HLD presents with 4 days of worsening left leg erythema, swelling, fever, and malaise following a minor abrasion. Pt was found to have MSSA endocarditis (mitral valve vegetation), surgery consulted and patient found to not be a surgical candidate.

- Patient was started on nafcillin 2g IV Q4h three weeks ago. Repeat blood cx negative, plan to continue regimen for 6 weeks.
- On week 3 (day 21), patient reports not feeling well.
- Vitals: BP 118/74, HR 87, RR 18, O_2 Sat 99% on RA, Temp 99.6 F
- Labs: WBC 10, SCr 1.9 (baseline 0.6), ALT 178, AST 156

Assessment Question #1: Pharmacist/Nurse

Day 21: Patient reports worsening pain and redness at his IV site requiring his third line placement for this admission. Based on clinical signs, symptoms, and lab results, which adverse effects are associated with the patient's current antibiotic regimen? (select all that apply)

A. Phlebitis
B. Acute interstitial nephritis
C. Thrombocytopenia
D. Hepatotoxicity

Assessment Question #1: Pharmacist/Nurse - Correct Response

Day 21: Patient reports worsening pain and redness at his IV site requiring his third line placement for this admission. Based on clinical signs, symptoms, and lab results, which adverse effects are associated with the patient's current antibiotic regimen? (select all that apply)

A. **Phlebitis**
B. **Acute interstitial nephritis**
C. Thrombocytopenia
D. **Hepatotoxicity**

Assessment Question #2: Pharmacist/Nurse

What is the most appropriate next step to take?

A. D/c nafcillin; switch to oxacillin
B. Continue nafcillin; toxicities are expected and reversible
C. D/c nafcillin; switch to cefazolin
D. D/c nafcillin; switch to ceftriaxone

Assessment Question #2: Pharmacist/Nurse - Correct Response

What is the most appropriate next step to take?

A. D/c nafcillin; switch to oxacillin

B. Continue nafcillin; toxicities are expected and reversible

C. D/c nafcillin; switch to cefazolin

D. D/c nafcillin; switch to ceftriaxone

Assessment Question #3: Pharmacy Tech

The patient is switched to cefazolin 2000 mg IV Q8h. What fluid should this medication be prepared in?

A. Sterile water for injection
B. ½ Normal Saline (0.45% NS)
C. D5W
D. Normal Saline (0.9% NS)

Assessment Question #3: Pharmacy Tech – Correct Response

The patient is switched to cefazolin 2000 mg IV Q8h. What fluid should this medication be prepared in?

A. Sterile water for injection
B. ½ Normal Saline (0.45% NS)
C. D5W
D. **Normal Saline (0.9% NS)**

Key Takeaways: ASPs vs. Cefazolin

Cefazolin and ASPs demonstrate comparable efficacy in the treatment of MSSA bacteremia

ASPs are associated with **higher** incidence of **nephrotoxicity** – use caution in patients with renal impairment

Cefazolin use has been associated with lower risk of mortality compared to ASPs

Alternative Treatments: Non-ASP Antibiotics

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Ceftriaxone: Outpatient Parenteral Antimicrobial Therapy

Recurrence rates of Methicillin Susceptible Staph aureus bacteremia after completion of antistaphylococcal therapy ranges from 5%-35% – this results in the need for extended duration of parenteral therapy

Cefazolin and Ceftriaxone were thought to have similar rates of treatment failure and known to have lower numbers of adverse events when compared to antistaphylococcal penicillins

Cefazolin has been shown in vitro to be subject to an inoculum effect due to hydrolysis by S. aureus beta-lactamases – Ceftriaxone does not suffer from this same inoculum effect – but this in vitro finding hasn't translated to clinical outcomes

IDSA recommends ≥2 weeks IV for uncomplicated MSSA bacteremia, 4–6 weeks for complicated, extended parenteral therapy is the standard, which makes agent selection for OPAT a critical decision

Sources: Carr et al. Open Forum Infect Dis. 2018
Liu C, et al. Clin Infect Dis. 2011;52(3):e18-55.
Baddour LM, et al. Circulation. 2015;132(15):1435-1486.
Kaasch AJ, et al. Lancet Infect Dis. 2024;24(5):523-534.

Ceftriaxone: Efficacy vs. Convenience

Appeal of Ceftriaxone

- Convenient Q24h dosing
- Ideal for OPAT settings
- Avoids Q8h cefazolin or continuous nafcillin infusions
- Simplified nursing and patient burden
- Lower direct drug cost per course

The Problems

Not recommended by IDSA as first-line for MSSA bacteremia

Higher treatment failure rates in clinical studies

Broader spectrum increases collateral damage risk

Highly Protein Bound

Low free drug concentrations at infection sites

Source: Tong SYC, et al. JAMA. 2025;334(9):798-808.

Ceftriaxone: Pharmacokinetic Limitations

~95%

Protein Bound

vs.. 74-86% for cefazolin

Parameter	Cefazolin	Ceftriaxone
Protein Binding	74-86%	~95%
Free Drug	~14-26%	~5%
Dosing Frequency	Q8H	Q24H
Pharmacodynamics	Time Dependent	Time Dependent

Why Protein Binding Matters

- Only free (unbound) drug exerts antimicrobial activity
- With ~95% of ceftriaxone bound to albumin, only ~5% circulates as active drug
- For deep-seated infections like endocarditis, osteomyelitis, and septic joints, this results in subtherapeutic concentrations at the site of infection

Sources: Cefazolin [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2021.
Ceftriaxone for Injection [package insert]. Lake Forest, IL: Hospira, Inc.; 2024.

Ceftriaxone vs. Cefazolin: Key Question

Do Ceftriaxone and Cefazolin have comparable treatment failure rates?

Ceftriaxone vs. Cefazolin: Carr et al. (2018)

Design:

- N = 71; Retrospective cohort, single-center VA Medical Center
- Cefazolin (n=38) vs.. Ceftriaxone (n=33)
- Population: MSSA bacteremia patients receiving ≥14 days parenteral therapy
- Study period: January 2009 – August 2014

Results:

- Primary (Treatment Failure): Cefazolin 28.9% vs.. Ceftriaxone 54.5%, P = 0.029
- Failure defined as: unplanned abx extension, relapse within 90 days, readmission, or surgical re-intervention

Key Finding: Ceftriaxone nearly DOUBLED treatment failure rate despite lower drug acquisition cost

Source: Carr DR, et al. Open Forum Infect Dis. 2018;5(5):ofy089.

Ceftriaxone vs. Cefazolin: Yetmar et al. (2023)

Design:

- Multicenter retrospective cohort study (2018–2019)
- Population: Adults with MSSA bacteremia receiving ceftriaxone vs.. cefazolin/ASPs as definitive outpatient therapy (≥7 days)
- Primary Outcome: 90-day treatment failure (composite: mortality + microbiologic recurrence)
- Adjusted for: Charlson Comorbidity Index, duration of therapy, use of TEE

Results:

- Adjusted HR for treatment failure with ceftriaxone: 2.66 (95% CI: 1.15–6.12), P = 0.022
- Composite outcome included both all-cause mortality and microbiologic recurrence
- Multicenter design strengthens external validity beyond single-center Carr et al

Key Finding: 2.66-fold increased risk of 90-day treatment failure with ceftriaxone (multicenter confirmation)

Source: Yetmar ZA, et al. Eur J Clin Microbiol Infect Dis. 2023;42(4):423-430.

Ceftriaxone: Final Thoughts

Ceftriaxone offers dosing convenience with Q24H dosing, but the evidence consistently shows significantly higher treatment failure rates when compared to cefazolin in MSSA bacteremia

Key Takeaways:

- **Evidence:** Carr 54.5% vs. 28.9% (P=0.029); Yetmar HR 2.66 (P=0.022)
  - Both show significantly higher treatment failure with ceftriaxone
- **Mechanism:** ~95% protein binding results in low free drug at deep infection sites
- **Cost:** Lower acquisition cost is offset by readmissions, prolonged hospitalization, and resistance pressure from broader-spectrum exposure
- **Bottom line:** Reserve ceftriaxone for cases where Q8h dosing is truly not feasible, after risk-benefit discussion

Sources: Carr DR, et al. Open Forum Infect Dis. 2018;5(5):ofy089.
Yetmar ZA, et al. Eur J Clin Microbiol Infect Dis. 2023;42(4):423-430.

Cefepime: Broad Spectrum Does Not Equal Better Coverage

Pathogen	1st Gen (Cefazolin)	3rd Gen (Ceftriaxone)	4th Gen (Cefepime)
Gram Positive	+++++	+++	+++
Gram-Negative	+	++++	+++++
Pseudomonal	-	-	++++
Anti-staphylococcal Optimization	HIGH	LOW	LOW

PBP-1 & 2 are the primary transpeptidase target for S. aureus cell wall synthesis

Cefazolin

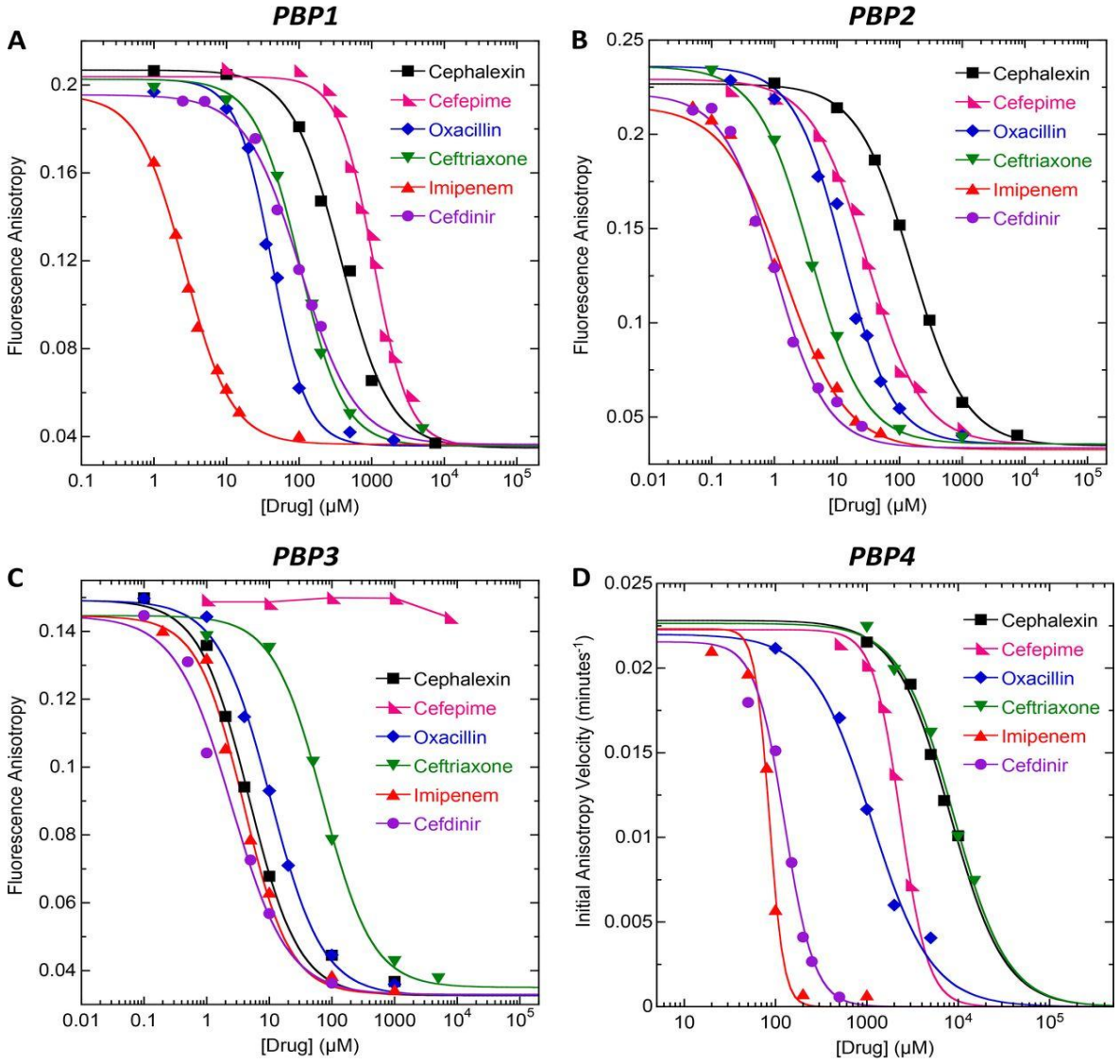
- Narrow spectrum targeting Gram-positive organisms
- High PBP-1, 2 & 3 binding affinity results in rapid bactericidal killing of S. aureus

Cefepime

- Engineered for enhanced Gram-negative PBP-3 binding (Pseudomonas)
- Structural modifications to gain GNR activity resulting in Staph aureus PBP binding that is PBP-2 selective

Source: Endimiani A, et al. Expert Rev Anti Infect Ther. 2008 Dec;6(6):805-24

PBP Binding Affinity in S. aureus: IC50



Abx	PBP-1	PBP-2	PBP-3	PBP-4
1st Gen	374	154	4.7	8,108
3rd Gen	100	3.8	71.9	8,906
4th Gen	1,059	30.3	>7,500	2,346
ASP	42.2	12.6	10.4	1,128

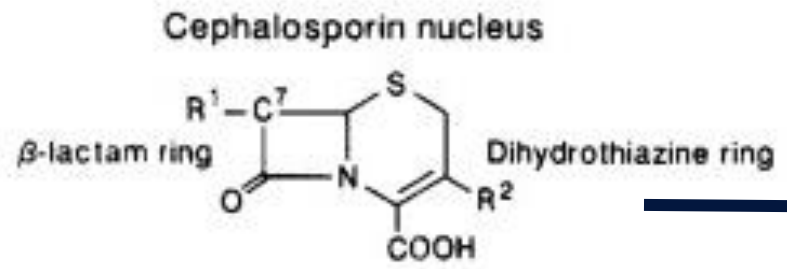
μM: Lower number = Higher affinity = Tighter binding to that PBP

Cefepime binds only to PBP-2 in S. aureus

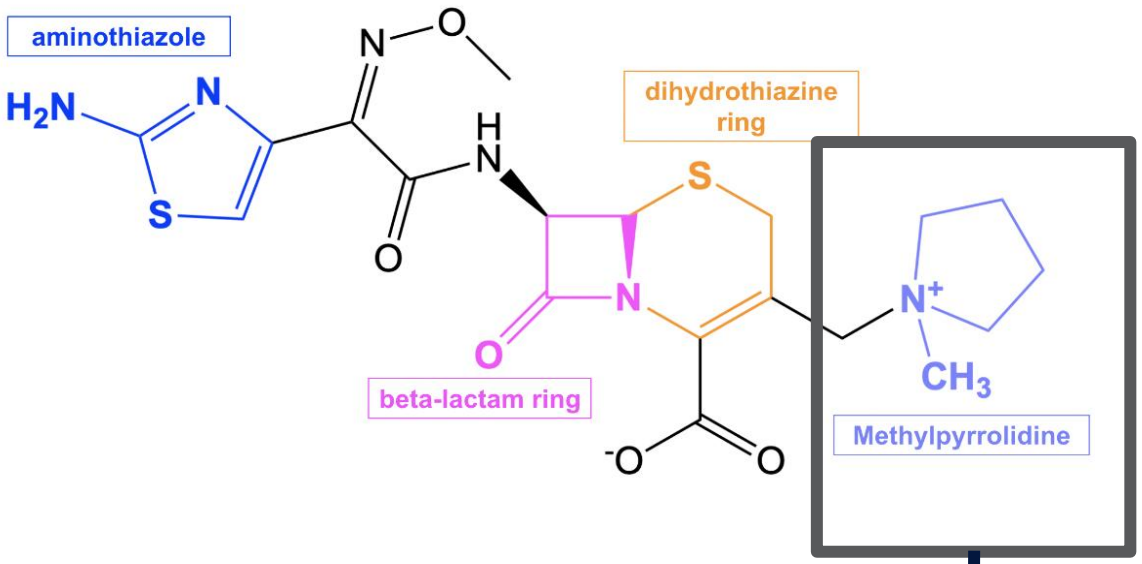
- PBP-1: IC50 of 1,059 ~25x weaker than oxacillin – essentially no binding
- PBP-2: IC50 of 30.3 – only meaningful S. aureus target
- PBP-3: IC50 of >7,500 – binding was so weak it wasn't fit on the curve

Sources: Ferrer-González E, Kaul M, Parhi AK, LaVoie EJ, Pilch DS. Antimicrob Agents Chemother. 2017;61(9):e00863-17. Table 2 & Figure 3: S. aureus PBP IC_{50} data. μM (micromolar) = micromoles per liter.

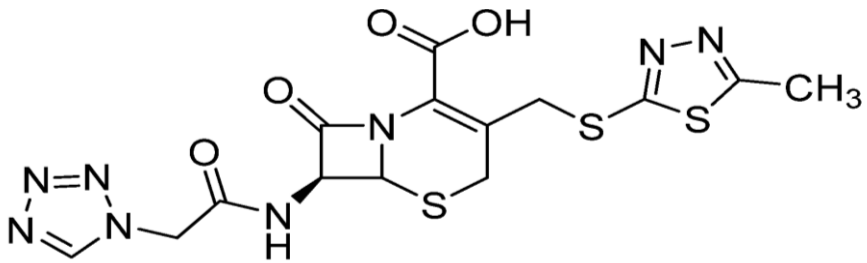
Cefepime: Structural Differences



Cefepime



Cefazolin



Methylpyrrolidinium group:
allows cefepime to rapidly penetrate through protein channels on the outer membrane of gram-negative bacteria, but this is a feature designed for organisms other than S. aureus.

This is due to the Zwitterionic charge which enhances bactericidal activity against gram-negatives

Source: Endimiani A, et al. Expert Rev Anti Infect Ther. 2008 Dec;6(6):805-24

Cefepime vs. Cefazolin: Key Question

Does Cefepime offer any clinical advantages over Cefazolin in the treatment of MSSA bacteremia?

Cefepime vs. Cefazolin: Fielding, et al. (2025)

Design:

- Single-center, retrospective cohort at University of Florida Health Shands Hospital (1162-bed academic center)
- N = 100 (50 APBL vs. 50 SOC), matched 1:1 on age, endovascular infection, and vasopressor use
  - APBLs = cefepime, pip-tazo, or meropenem; SOC = cefazolin or oxacillin
- Study period: June 2016 – June 2023
- ≥14 consecutive days of inpatient therapy
- Primary outcome: Composite clinical failure (30-day all-cause mortality + bacteremia recurrence within 30 days)

Results:

- APBL 6% vs. SOC 2%, p = 0.62 — NOT significant
- No significant differences in any secondary outcomes (60-day mortality, ICU LOS, hospital LOS, 30-day readmission, time to clearance, C. diff, AKI, hepatotoxicity)

Key Finding: No differences in mortality or bacteremia recurrence were identified - underpowered – included agents other than cefepime

Source: Fielding M, et al. Ther Adv Infect Dis. 2025;12:20499361251395527.

Cefepime: Consequences of Continuation

Continuing broad-spectrum agents after MSSA confirmation provides no clinical benefit while increasing risk of:

- Clostridioides difficile infection
- VRE colonization and superinfection
- ESBL-producing Enterobacterales selection
- Depletion of cefepime as an empiric antipseudomonal option

Cefepime is associated with increased neurotoxicity & encephalopathy risk

Sources: Patterson DL. Clin Infect Dis. 2004;38 Suppl 4:S341-5
Cefazolin [package insert]. Deerfield, IL: Baxter Healthcare Corporation; 2021.
Maxipime (cefepime hydrochloride) [package insert]. Lake Forest, IL: Hospira, Inc.; 2020.

Cefepime: Final Thoughts

Cefepime offers no demonstrated clinical advantage over cefazolin for MSSA bacteremia, while adding spectrum, neurotoxicity risk, and stewardship cost

Key Takeaways:

- **Mechanism:** Cefepime's PBP-2 selectivity sacrifices the multi-PBP engagement that cefazolin provides
- **Evidence:** Fielding 2025 found no clinical benefit (APBL 6% vs. SOC 2%, p=0.62)
- **Safety:** Cefepime's package insert specifically highlights the increased risk for neurotoxicity – specifically in patients with renal failure, cefazolin has no comparable risk noted in its package insert
- **Bottom line:** De-escalate to cefazolin once MSSA confirmed, reserve cefepime for confirmed/suspected Pseudomonas

Sources: Fielding M, et al. Ther Adv Infect Dis. 2025;12:20499361251395527.
Ferrer-González E, et al. Antimicrob Agents Chemother. 2017;61(9):e00863-17.

Vancomycin: De-escalation

Despite guideline recommendations, vancomycin continues to be used for definitive MSSA therapy in clinical practice.

IDSA and treatment guidelines recommend prompt de-escalation from vancomycin to a beta-lactam upon MSSA identification.

Beta-Lactams (Cefazolin)	Vancomycin
• Actively bactericidal • Rapid cell lysis • Time-dependent killing	• Slowly bactericidal • Depends on AUC/Trough targets • Targets often missed in practice

Sources: McDanel JS, et al. Clin Infect Dis. 2015;61(3):361-7.
Liu C, et al. Clin Infect Dis. 2011;52(3):e18-e55.

Vancomycin vs. Cefazolin: Key Question

Once MSSA is confirmed, is there any clinical reason to continue vancomycin instead of de-escalating to cefazolin?

Vancomycin vs. Cefazolin/ASP: McDanel, et al. (2015)

Design:

- N = 5,787; Retrospective cohort across 122 VA hospitals (largest study to date)
- Population: Patients with MSSA bloodstream infections
- Empiric (started 2 days before to 4 days after first culture) vs. Definitive therapy (started 4-14 days after first positive culture)
- Primary outcome: 30-day all-cause mortality

Results:

- Empiric therapy: β-lactam vs. vancomycin – no mortality difference (HR 1.03; 95% CI 0.89-1.20)
- Definitive therapy: β-lactam = 35% lower mortality vs. vancomycin (HR 0.65; 95% CI 0.52-0.80)
- Cefazolin or ASPs specifically: 43% lower mortality vs. vancomycin (HR 0.57; 95% CI 0.46-0.71)

Key Finding: Significant mortality reduction associated with de-escalating from vancomycin to targeted beta-lactam therapy

Source: McDanel et al. Clin Infect Dis. 2015

Vancomycin: Consequences of Continuation

Continuation of vancomycin in patients with verified MSSA provides no additional benefit and instead increases the risk of the following:

Slower Bacteremia Clearance	Increased Mortality When Used as Definitive Therapy	Nephrotoxicity & Ototoxicity Risk
Requirement of AUC/MIC Monitoring	Increased Superinfection/VRE Risk	Infusion Reactions Risk

These issues result in increased cost associated with vancomycin use

The use of Vancomycin should be limited to empiric purposes in patients with history of risk factors for MRSA

Sources: Rybak, Michael American Journal of Health-System Pharmacy: AJHP vol. 77,11 (2020): 835-864.
Wong D, et al. Eur J Clin Microbiol Infect Dis. 2016;35(10):1755-1759.

Vancomycin: MRSA Risk Factors

Health Care Exposures in the Last 12 Months

- Recent hospitalization
- Residence in a long-term care facility
- Recent surgery
- Hemodialysis

Patient Specific Risk Factors

- Known MRSA colonization or past infection with MRSA
- Recent close contact with a person colonized or infected with MRSA
- HIV infection
- Injection drug use
- Antibiotic use within prior 6 months

Vancomycin: Final Thoughts

Vancomycin is appropriate empirically when MRSA is a concern, but continued use after MSSA confirmation is associated with significantly increased mortality

Key Takeaways:

- **Mechanism:** Slowly bactericidal with AUC/MIC-dependent killing
- **Evidence:** McDanel 2015 demonstrated 35-43% mortality reduction with cefazolin/ASPs vs. vancomycin as definitive therapy
- **Safety:** Vancomycin is associated with risk of nephrotoxicity, infusion reactions, and requires close AUC/MIC monitoring
- **Bottom Line:** De-escalate to cefazolin once MSSA is confirmed – continued vancomycin does not provide benefit

Sources: McDanel JS, et al. Clin Infect Dis. 2015;61(3):361-7.
Liu C, et al. Clin Infect Dis. 2011;52(3):e18-e55.
Wong D, et al. Eur J Clin Microbiol Infect Dis. 2016;35(10):1755-1759.

Assessment Question #4: Pharmacy Tech

72 yo F with PMH significant for CHF, HTN, and MI (3 years prior) diagnosed with MSSA bacteremia secondary to a skin abscess. The infectious disease team recommends cefazolin 2 g IV every 8 hours as definitive therapy. Which of the following BEST describes an advantage of cefazolin over nafcillin for this patient?

A. Cefazolin has superior bactericidal activity against all MSSA strains compared to nafcillin
B. Cefazolin is not susceptible to hydrolysis by staphylococcal β-lactamases
C. Cefazolin is associated with significantly lower rates of nephrotoxicity and hepatotoxicity compared to antistaphylococcal penicillins
D. Cefazolin achieves higher CNS penetration than nafcillin, making it preferred for CNS infections

Assessment Question #4: Pharmacy Tech – Correct Response

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Assessment Question #5: Pharmacy Tech

A hospitalized patient with MSSA osteomyelitis is being transitioned to outpatient parenteral antibiotic therapy (OPAT). What are the pros and cons of using ceftriaxone for MSSA bacteremia?

A. Ceftriaxone has no role in MSSA treatment because it lacks gram-positive activity entirely
B. Ceftriaxone offers once-daily dosing convenience but has inferior pharmacodynamic activity against MSSA
C. Ceftriaxone is the preferred agent for MSSA OPAT per current guidelines due to its long half-life and superior clinical outcomes
D. Ceftriaxone has equivalent pharmacodynamic activity to cefazolin but carries a higher risk of C. difficile infection

Assessment Question #5: Pharmacy Tech – Correct Response

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Assessment Question #6: Pharmacist/Nurse

A 45-year-old woman with MSSA native valve endocarditis is being treated with cefazolin. The microbiology lab reports that her MSSA isolate demonstrates a cefazolin inoculum effect (CzIE),with the cefazolin MIC rising from 1 µg/mL at standard inoculum to 32 µg/mL at high inoculum. Which of the following BEST describes the clinical significance of this finding?

A. The inoculum effect is a real in vitro phenomenon, but clinical data have not demonstrated a significant impact on mortality
B. The inoculum effect is mediated by the blaZ gene and is associated with increased mortality, requiring a switch to nafcillin
C. The inoculum effect affects all β-lactams equally, so switching to nafcillin would not help
D. The inoculum effect only occurs with type B β-lactamases and is rare in North America

Assessment Question #6: Pharmacist/Nurse - Correct Response

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Other Considerations

Safety

Nafcillin

- Acute interstitial nephritis
- Hepatotoxicity (elevated AST/ALT)
- Phlebitis (frequent IV site changes)
- Bone Marrow Suppression
- Q4H Dosing Burden

Vancomycin

- Nephrotoxicity
- Ototoxicity
- Requires close monitoring of levels
- Drug-drug interactions with other nephrotoxins
- Vancomycin infusion reaction

Cefazolin

- Low nephrotoxicity risk
- No hepatotoxicity
- Minimal phlebitis
- Q8H Dosing is better tolerated

Sources: Cefazolin, Nafcillin, Vancomycin package inserts. Accessed Feb 2026.

Stewardship

Why Cefazolin in MSSA bacteremia?

Efficacy

Superior or equivalent outcomes compared to all alternatives

Safety

Avoids nephrotoxicity (vancomycin), hepatotoxicity/AIN (nafcillin), and requires no drug level monitoring

Cost

One of the most inexpensive IV antibiotics on formulary; minimal hidden costs from monitoring or ADE management

Resistance Mitigation

Narrow spectrum preserves broad-spectrum agents, reduces C. difficile risk, and limits VRE/ESBL selection pressure

Recommendations

- Optimize therapy by selecting the narrowest effective antimicrobial agent
- Cefazolin is preferred first-line therapy for most cases of MSSA bacteremia
- In suspected or confirmed central nervous system involvement, consider ASPs
- Individualize treatment decisions based on patient-specific factors, weighing risks and benefits

Thank You!

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