UPMC LIFE CHANGING MEDICINE

Low Albumin, High Stakes:

The Management of MSSA Bacteremia Treatment Options and Impact of Hypoalbuminemia

Rachel Marini, PharmD, BCIDP

Infectious Diseases Pharmacist

marinirv2@UPMC.edu

Slides adopted from Dr. Sunish Shah, PharmD, BCIDP

Learning Objective

- Evaluate factors associated with optimal antimicrobial selection for the treatment of MSSA bacteremia

Patient Case

- 49-year-old male with a history of complete heart block requiring a permanent cardiac pacemaker presented to the emergency department with a 3-day history of fever, chills, generalized weakness, and increasing shortness of breath.

- On admission, febrile to **39.2°C**, tachycardic (**HR 115 bpm**), hypotensive (BP 88/54 mmHg), and had a **WBC count of 18,000** cells/mm^3 with an elevated lactate of 3.8 mmol/L.

- Blood cultures were obtained, and broad-spectrum antibiotics were initiated for suspected sepsis and **CIED infection.**

Patient Case

- 12hours after admission, blood culture data available from rapid diagnostic system called to stewardship team…….

STAPHYLOCOCCUS AUREUS

	MIC (mcg/mL)	MIC Interpretation
Clindamycin	<=0.25	Sensitive
Daptomycin	<=0.25	Sensitive
Gentamicin	<=1	Sensitive
Linezolid	2	Sensitive
Oxacillin	<=0.25	Sensitive
Rifampin	<=1	Sensitive
Rifampin should not be used alone for therapy.		
Sulfa/Trimethoprim	<=0.5/9.5	Sensitive
Tetracycline	<=2	Sensitive
Vancomycin	0.5	Sensitive

Last Update: 8/03/26 9:31 AM
Collected: 8/02/26 10:18 AM

BLOOD PCR GRAM P[redacted]

Status: **Final**

BOTTLE TYPE: Testing performed on anaerobic bottle.

REFLEXED FROM x15210497

INTERPRETATION:

Results suggest methicillin SUSCEPTIBLE Staphylococcus aureus (MSSA).

BACILLUS SUBTILIS:	Not Detected
BACILLUS CEREUS:	Not Detected
CORYNEBACTERIUM SPECIES:	Not Detected
CUTIBACTERIUM ACNES (P.ACNES):	Not Detected
ENTEROCOCCUS SPECIES:	Not Detected
ENTEROCOCCUS FAECALIS:	Not Detected
ENTEROCOCCUS FAECIUM:	Not Detected
LACTOBACILLUS SPECIES:	Not Detected
LISTERIA SPECIES:	Not Detected
LISTERIA MONOCYTOGENES:	Not Detected
MICROCOCCUS SPECIES:	Not Detected
STAPHYLOCOCCUS SPECIES:	DETECTED
STAPHYLOCOCCUS AUREUS:	DETECTED
STAPHYLOCOCCUS EPIDERMIDIS:	Not Detected
STAPHYLOCOCCUS LUGDUNENSIS:	Not Detected
STREPTOCOCCUS SPECIES:	Not Detected
STREPTOCOCCUS AGALACTIAE:	Not Detected
STREPTOCOCCUS ANGINOSUS:	Not Detected
STREPTOCOCCUS PNEUMONIAE:	Not Detected
STREPTOCOCCUS PYOGENES:	Not Detected
PAN GRAM NEGATIVE:	Not Detected
PAN CANDIDA:	Not Detected
VANB:	Not Applicable
VANA:	Not Applicable
MECC:	Not Detected
MECA:	Not Detected

Diary from Stewardship Team Member…..

Which antimicrobial is the best to select?

Do I need to consider combination therapy?

What is the best dose for this infection?

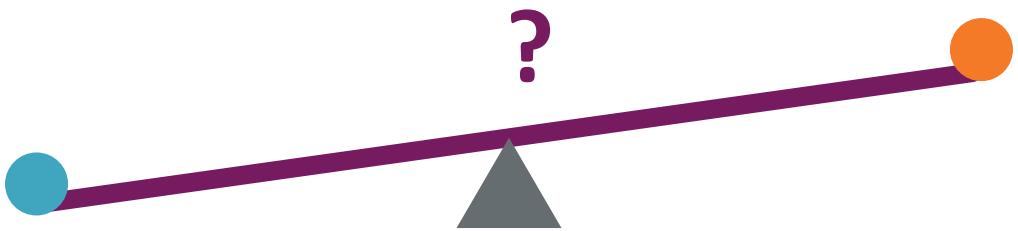
MSSA DOC?

Anti-staphylococcal PCN

- May have more ADRs
- Renal dosing adjustments not indicated
- Believed to be stable in inoculum effect
- Data supporting CNS concentrations

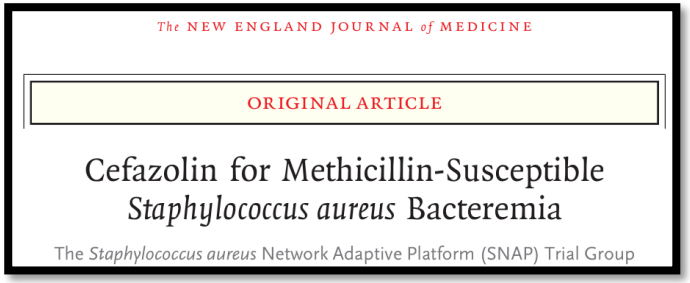
Cefazolin

- Associated with fewer ADRs
- Well tolerated, but does require renal dosing adjustments
- Concerns of stability in inoculum effect cases
- Historic concerns of CNS concentrations



UPMC LIFE CHANGING MEDICINE

2026 SNAP Trial


The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cefazolin for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Trial Group

Design	One domain of the Bayesian adaptive platform to address agent selection question *Open-label, randomized, noninferiority comparison of cefazolin vs antistaphyloccal penicillin*
Population	Hospitalized patients with *S. aureus* BSI enrolled within 72h after collection of the index blood culture
Exclusion	Polymicrobial bacteremia, treatment limitations (EOL or allergies), dialysis or concomitant systemic antimicrobials. ONLY patients with PCN-resistant MSSA (inoculum effect)
Intervention	1:1 randomization **cefazolin** 2g q8h (q6h if EVI or critical ill) vs **flucloxacillin or cloxacillin**

NEJM. 2026 Jun 18;394:2329-2339

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Cefazolin for Methicillin-Susceptible *Staphylococcus aureus* Bacteremia

The *Staphylococcus aureus* Network Adaptive Platform (SNAP) Trial Group

Primary focus/ type of infection:

- Osteoarticular infection
  - 32.8% [C] vs 21.3% [F/C]
- SSTI
  - 26.4% [C] vs 30.4% [F/C]

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Cefazolin (N=671)	Flucloxacillin or Cloxacillin (N=670)
Demographic characteristics		
Median age (IQR) — yr	66 (53–76)	66 (52–77)
Female sex — no. (%)	215 (32.0)	206 (30.7)
Median weight (IQR) — kg	82.0 (69.0–96.8)	80.0 (68.0–95.0)
Coexisting conditions — no. (%)		
Diabetes mellitus	231 (34.4)	217 (32.4)
Chronic kidney disease†	96 (14.3)	93 (13.9)
Cirrhosis	34 (5.1)	30 (4.5)
Cancer leading to any surgical or medical therapy within past 12 mo‡	95 (14.2)	76 (11.3)
Dementia	23 (3.4)	32 (4.8)
Iatrogenic immunosuppression§	105 (15.6)	84 (12.5)
Implanted intravascular prosthesis or endovascular device¶	64 (9.5)	58 (8.7)
Previous infective endocarditis	11 (1.6)	10 (1.5)
Underlying cardiac abnormality conferring predisposition to endocarditis‖	50 (7.5)	42 (6.3)
Injection drug use within past 6 mo	31 (4.6)	52 (7.8)
Limitations to care**	80 (11.9)	84 (12.5)

NEJM. 2026 Jun 18;394:2329-2339

2026 SNAP Trial

Outcome	Cefazolin n= 671	Flucloxacillin/ cloxacillin n=670	Odds Ratio (95% CrI)	Prob. of noninferiority	Prob. of superiority
Death from any cause within 90 days (primary analysis)	97/645 (15%)	109/624 (17%)	0.81 (0.59 – 1.12)	99.2	89.8
Any serious ADR related to trial drug	12/671 (1.8%)	33/670 (4.9%)	0.41 (0.21 – 0.77)	99.9	99.8
Death by 14 days	25/667 (3.7%)	37/665 (5.6%)	0.67 (0.39 – 1.11)	-	-
Death by 42 days	63/663 (9.5%)	86/662 (13%)	0.66 (0.46 – 0.94)	-	-
Change of antibiotic from ADR	11/671 (1.6%)	61/670 (9.1%)	0.21 (0.11 – 0.38)	-	-

Author Conclusions: cefazolin was noninferior to flucloxacillin/cloxacillin for 90-day mortality and was associated with lower rates of AKI

NEJM. 2026 Jun 18;394:2329-2339

Antimicrobial Regimen

☑Optimal agent for MSSA treatment

❑**When to consider combination therapy**

❑What is the optimal dose

Optimizing Cefazolin

- Previous Literature - MSSA bacteremia
  - 90-day mortality
    - **22%** with 1 day of bacteremia and **39–43%** with ≥2–7 days

      Kuehl R et al. Lancet Infect Dis. 2020 Dec;20(12):1409-1417.

  - Could combination therapy optimize this?
    - Ertapenem demonstrates higher affinity for **PBP1** than cefazolin, while cefazolin is further selective for **PBP2**

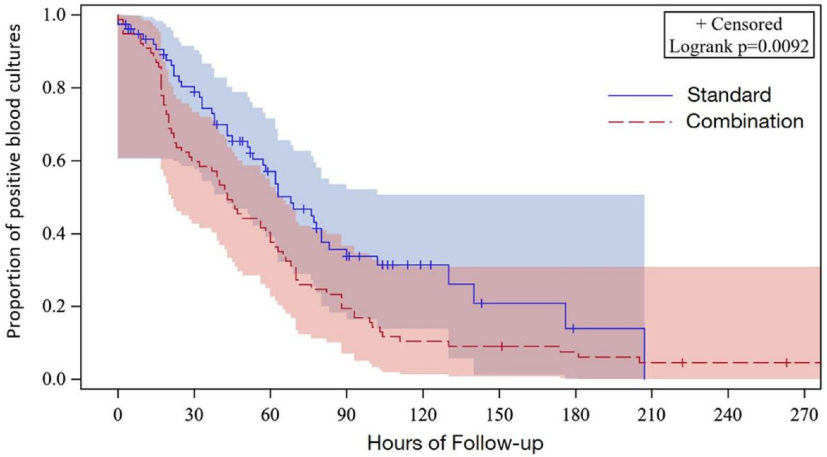
      Sakoulas G et al. Antimicrob Agents Chemother. 2016 Oct 21;60(11):6609-6618

UPMC LIFE CHANGING MEDICINE

Carbapenem combination therapy versus standard of care for persistent methicillin-susceptible *Staphylococcus aureus* bacteraemia

Sunish Shah [1,2]*, Lloyd G. Clarke[1,2], Justin Ludwig[3], Sarah Burgdorf[4], Ricardo D. Arbulu Guerra[4] and Ryan K. Shields [1,4]

- 238 patients were included
  - After applying risk-set matching of combination therapy versus standard care
    - combination therapy experienced faster time to blood culture sterilization
      - [HR = 1.618 (95% CI; 1.119–2.339) P = 0.011].
    - 90 day mortality rates not statistically different among
      - [HR = 1.267 (95% CI; 0.610–2.678), P = 0.608]



J Antimicrob Chemother. 2024 Aug 1;79(8):1990-1997

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy

Check for updates

Antimicrobial Chemotherapy | Full-Length Text

Incidence and factors associated with rapid blood culture sterilization among patients receiving ertapenem combination therapy for MSSA bacteremia

Sunish Shah,[1,2] Lloyd G. Clarke,[1,2] Bonnie A. Falcione,[1,2,3,4] Ryan K. Shields,[1,4] Brandon J. Smith[1,4]

Antimicrob Agents Chemother. 2026 Feb 4;70(2):e0130325..

Blood culture sterilization occurred in 85-90% within **3 doses of ertapenem**

Impact of hypoalbuminemia on patients receiving ertapenem combination therapy for methicillin-susceptible *Staphylococcus aureus* bacteraemia

Sunish Shah [1,2]*, Lloyd G. Clarke[1,2], G. K. Balasubramani[3], Lingyi Peng[4], Brandon J. Smith[1,5] and Ryan K. Shields [1,5]

J Antimicrob Chemother. 2025 Jul 1;80(7):1823-1827.

- Longer time to negative blood cultures compared to patients with normal albumin levels
  - (HR=0.45, 95% CI: 0.27–0.72, *P* = 0.001)
- But why?
  - ASP or cefazolin (> 90% protein bound)
  - Ertapenem (> 90% protein bound)
  - Albumin definition

UPMC LIFE CHANGING MEDICINE

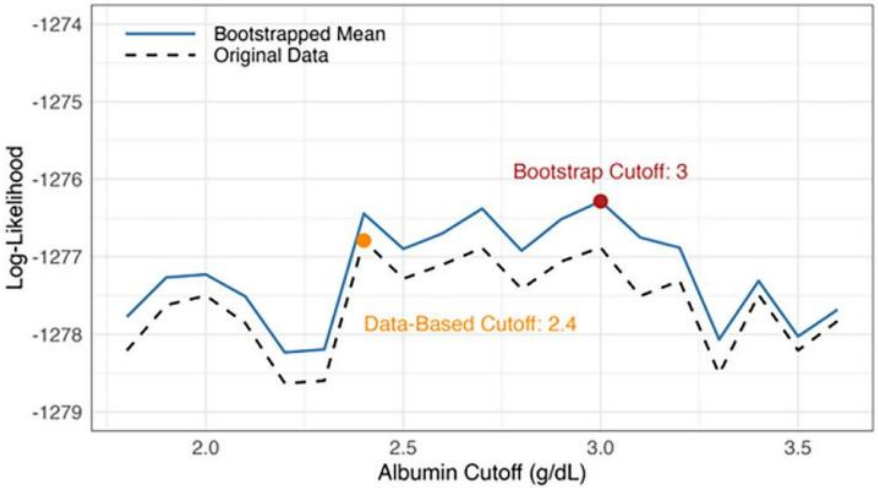
J Antimicrob Chemother 2026; **00**:
https://doi.org/10.1093/jac/dkaf498

Journal of Antimicrobial Chemotherapy 50 years

Evaluating hypoalbuminaemia thresholds associated with delayed blood sterilization among patients receiving cefazolin or antistaphylococcal penicillins for MSSA bacteraemia

Sunish Shah [1,2*], Lingyi Peng [3], Lloyd G. Clarke [1], G.K. Balasubramani [4], Brandon J. Smith [1,5] and Ryan K. Shields [1,5]

- 285 patients with persistent MSSA bacteremia
- Following PS weighting
  - Slower time to blood culture sterilization compared with patients with albumin levels >3 g/dL
    - (HR=0.6; 95% CI: 0.44–0.81; P<0.01).
  - Similar 90 day mortality rate compared with patients with albumin levels >3 g/dL
    - (OR=2.8; 95% CI: 0.78–9.75; P=0.12).



UPMC LIFE CHANGING MEDICINE

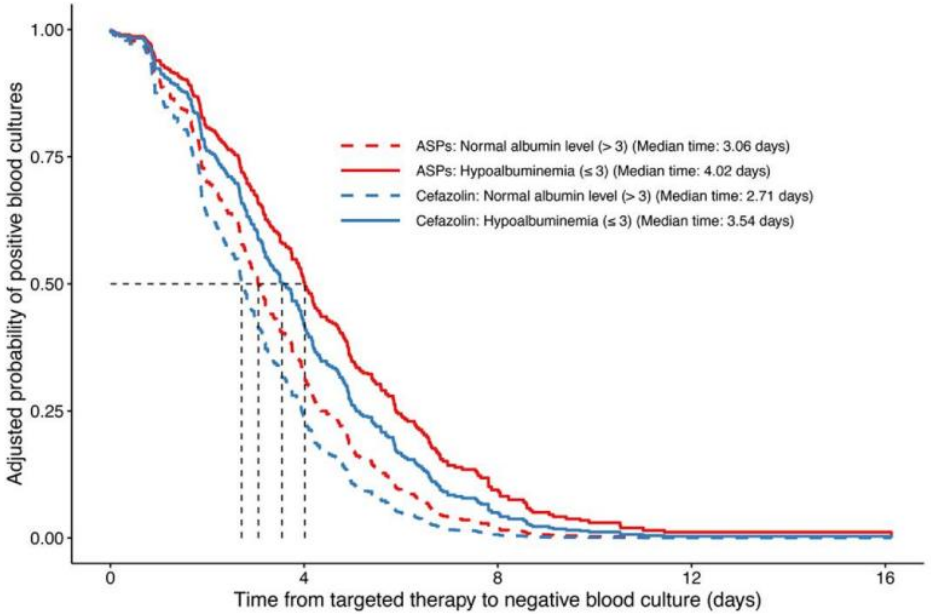
J Antimicrob Chemother 2026; **00**:
https://doi.org/10.1093/jac/dkaf498

Journal of Antimicrobial Chemotherapy 50 years

Evaluating hypoalbuminaemia thresholds associated with delayed blood sterilization among patients receiving cefazolin or antistaphylococcal penicillins for MSSA bacteraemia

Sunish Shah [1,2]*, Lingyi Peng [3], Lloyd G. Clarke [1], G.K. Balasubramani [4], Brandon J. Smith [1,5] and Ryan K. Shields [1,5]

- But why?
  - Underlying disease
    - Similar mortality rates but failure to sterilize
  - Antibiotic underexposure?
    - Should we be further dose optimizing and how?
    - What are our targets?
      - Guidelines are only as good as the data used to make recommendations
      - Cefazolin: 40-80 mcg/mL
      - Reference: Guilhaumou R et al. Crit Care. 2019 Mar 29;23(1):104.



 J Antimicrob Chemother. 2026 Jan 19;81(2):dkaf498.

UPMC LIFE CHANGING MEDICINE

UPMC PUH MSSA BSI Algorithm

MSSA BACTEREMIA

Initial Therapy: Cefazolin **OR** Oxacillin*

Perform daily blood cultures until documented clearance

Suspected HIGH-RISK Endovascular Infection?

High risk:
- Vasopressors
- Left sided vegetations > 1cm
- CIED that cannot be removed
- Prosthetic valves
- Multiple metastatic foci/undrainable abscesses
- Injection drug use

Blood culture clearance at 7 days?

YES → **Complete treatment course with oxacillin or cefazolin monotherapy**

NO

NO → **Conduct aggressive evaluation for foci of infection (e.g. TEE, MRI spine, nuclear medicine scans)**

Consider:
- Addition of Ertapenem

→ ***Ertapenem for 1-3 doses**

YES

NO → Add Ertapenem**

***No need to add gentamicin if using ertapenem for prosthetic valve infective endocarditis*

Blood culture clearance at 96 hours?

YES → **Complete treatment course with oxacillin or cefazolin monotherapy**

Notes
*70% of patients sterilize blood cultures after one ertapenem dose and 89% of patients after 3 doses
Can consider early initiation of ertapenem in patients with definitive endocarditis and persistent vasopressors

Reference: J Antimicrob Chemother. 2024 Aug 1;79(8):1990-1997.

UPMC LIFE CHANGING MEDICINE

Antimicrobial Regimen

☑Optimal agent for MSSA treatment

☑When to consider combination therapy

❑**What is the optimal dose**

J Antimicrob Chemother 2026; **81**: dkag232
https://doi.org/10.1093/jac/dkag232

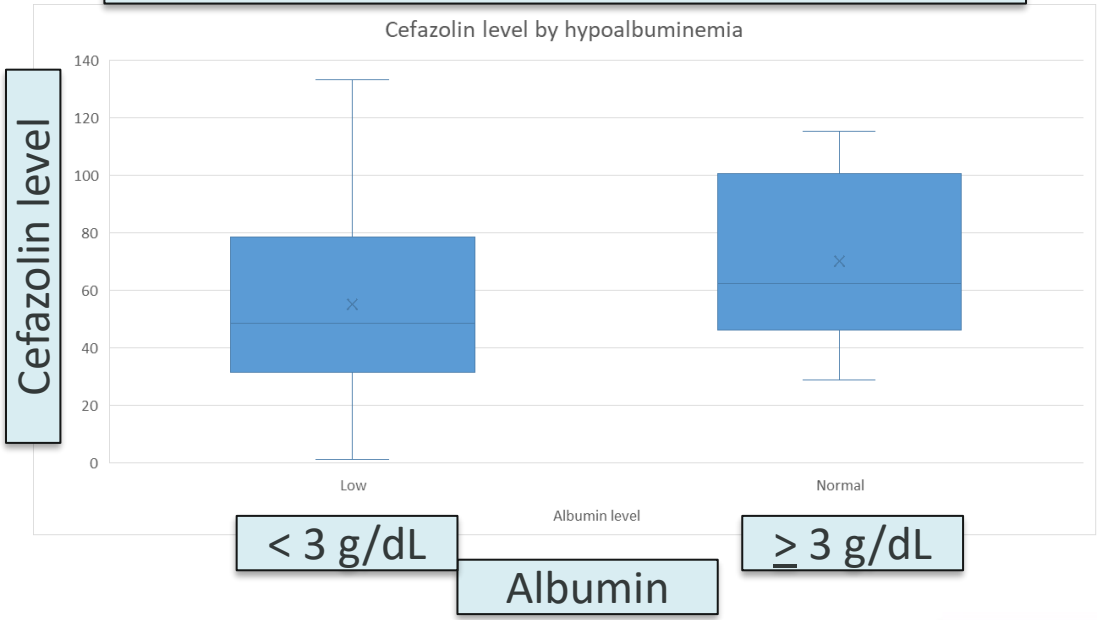
Journal of Antimicrobial Chemotherapy

Incidence and factors associated with subtherapeutic cefazolin levels among patients with severe infections

Sunish Shah [1,2*], Rachel V. Marini[1,3], Ryan K. Shields [1,3] and Brandon J. Smith[1,3]

- Seventy patients were included
- Overall, 76% (53/70) of patients had bloodstream infections
  - Of whom 60% (32/53) had definitive endocarditis
- **MSSA was the underlying pathogen in 86% (60/70) of cases**
- Subtherapeutic levels were observed in 39% (27/70) of patients

Hypoalbuminemia impact on cefazolin TDM



J Antimicrob Chemother. 2026 June 81; (8) dkag232.

UPMC LIFE CHANGING MEDICINE

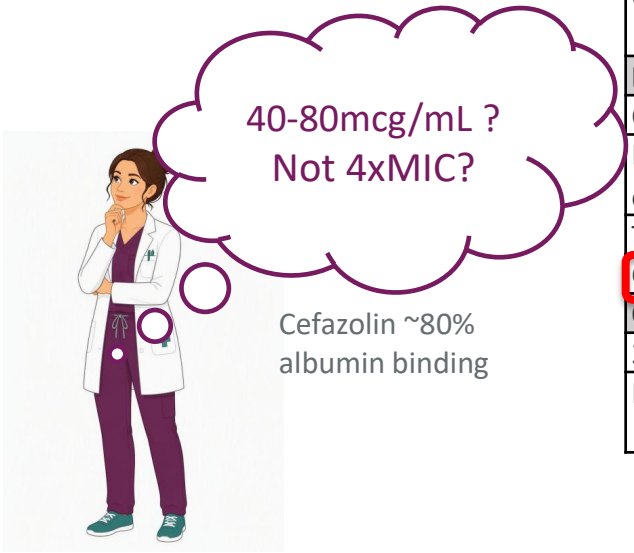
Continuous versus intermittent

	Continuous (n=48)	Intermittent[3] (n=22)	P-value
Baseline demographics			
Age, median (IQR)	63 (56-72)	66 (62-90)	0.234
Female, n (%)	19 (40)	10 (46)	0.644
Person who injects drugs, n (%)	4 (8)	0 (0)	0.301
Source control indicated but not received, n (%)	13 (27)	5 (23)	0.699
Methicillin susceptible *S. aureus*, n (%)	40 (83)	20 (91)	0.488
Critically ill, n (%)	15 (31)	5 (23)	0.574
Acute kidney injury, n (%)	13 (27)	4 (18)	0.553
Albumin level (g/dL), median (IQR)	N=38 2.6 (2.2-3)	N=17 2.4 (2.1-2.7)	0.093
Drug administration			
Total daily dose (grams), median (IQR)	6 (6-8)	6 (6-6)	0.271
Days from bacteremia to cefazolin initiation, median (IQR)	N=35 3 (1-10)	N=18 2 (1-3)	0.142
Outcomes			
In hospital mortality, n (%)	6 (13)	2 (9)	>0.999
30-days mortality, (%)	7 (15)	4 (18)	0.731
Cefazolin level (mcg/mL), median (IQR)	61 (38-80)	38 (19-71)	**0.012**
Post level length of stay, median (IQR)	N=46 5 (2-11)	N=22 9 (4-20)	0.099

Clinical outcomes challenging to design

J Antimicrob Chemother. 2026 June 81; (8) dkag232.

Factors associated with a level < 40 mcg/mL



	Subtherapeutic[1] (n=27)	Therapeutic or supratherapeutic (n=43)	P-value
Baseline demographics			
Endocarditis, n (%)	7 (26)	25 (58)	**0.008**
Critically ill, n (%)	4 (15)	16 (37)	0.058
Vasopressors, n (%)	0 (0)	8 (19)	**0.019**
Acute kidney injury, n (%)	2 (7)	15 (35)	**0.011**
Creatinine Clearance (mL/min)[3], median (IQR)	N=27 110 (90-136)	N=39 67 (43-100)	**0.004**
Drug administration			
Cefazolin level (mcg/mL), median (IQR)	32 (18-38)	73 (56-87)	**< 0.001**
Days from cefazolin initiation to level obtainment, median (IQR)	4.7 (3.5-9.6)	3.9 (1.9-5.8)	0.098
Total daily dose (grams), median (IQR)	6 (6-6)	6 (6-8)	0.974
Continuous, median (IQR)	14 (52)	34 (79)	**0.017**
Outcomes			
30-days mortality, (%)	2 (7)	9 (21)	0.184
Post level length of stay, median (IQR)	N=26 7 (1-15)	N=42 6 (3-12)	0.965

J Antimicrob Chemother. 2026 June 81; (8) dkag232.

Operationalizing TDM

- ✓ **Identify patients that may benefit from TDM**
  - Just because we *CAN* send a test, doesn't mean that we *SHOULD*
  - <albumin, deep seeded infections (EVI, CNS, etc), CI dosing, discordant renal function calculations, concern of treatment failure
- ✓ **Determine strategy for collection and send out process**
  - Collection on discharge dosing strategy, pause CI infusion (and flush line ☺), timing for results and adjustments
- ✓ **Interpretation and modification on case-by-case basis**
  - Target 40-80mcg/mL but many assumptions
  - Doses may be higher than standard algorithms

Audience Response

Which of the following should be considered when selecting an antimicrobial regimen for MSSA bacteremia?

- **A** Antimicrobial selection of drug based on side-effect profile
- **B** Hypoalbuminemia
- **C** Availability of therapeutic drug monitoring (TDM)
- **D** Availability of continuous infusion or extended-interval dosing
- **E** All of the above

Summary

Drug selection

- SNAP: cefazolin noninferior to antistaphylococcal penicillin for 90-day mortality (15% vs 17%)
- Fewer serious drug-related ADRs (1.8% vs 4.9%) and far fewer antibiotic changes (1.6% vs 9.1%)

Combination therapy

- Early ertapenem shortens time to blood culture clearance in persistent MSSA bacteremia
- 85–90% sterilize within 3 doses; 90-day mortality not significantly different

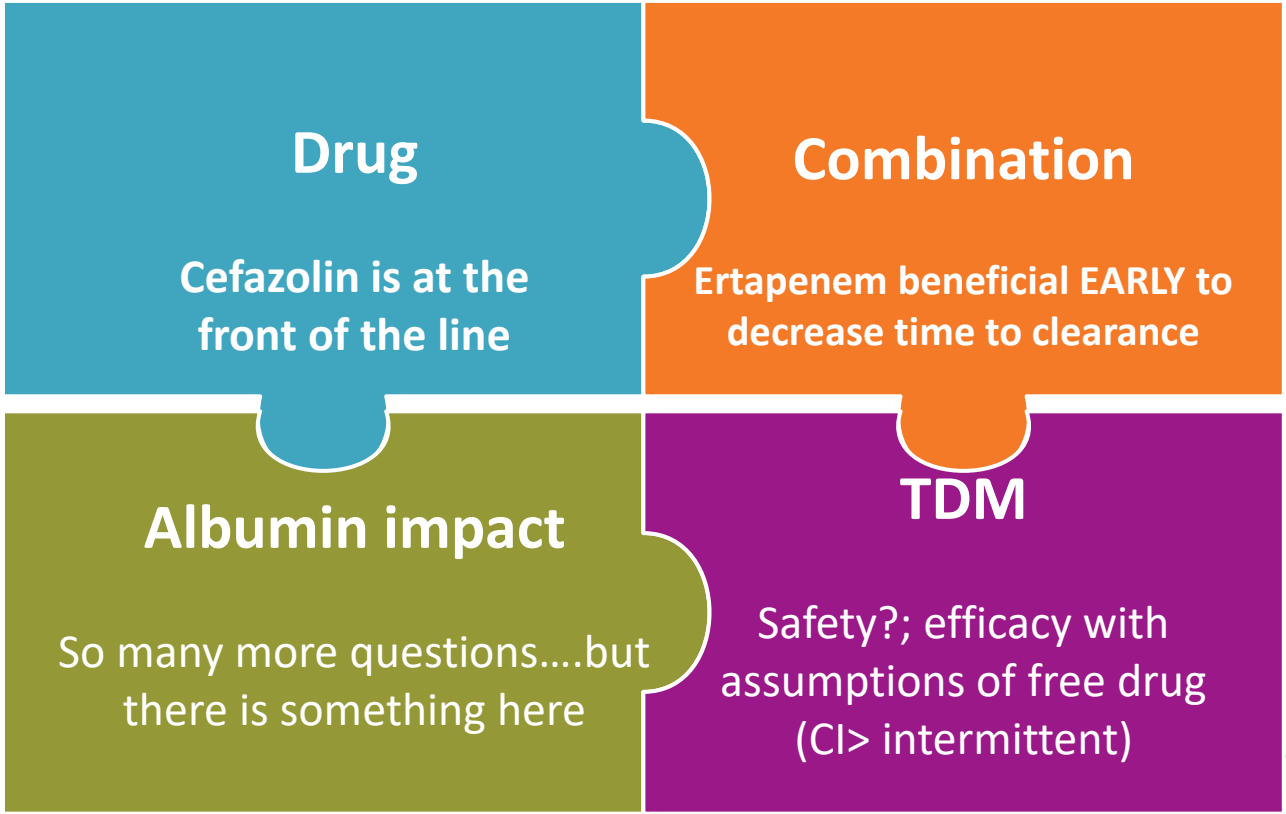
Hypoalbuminemia

- Albumin <3 g/dL is associated with slower blood culture clearance (HR 0.6; 95% CI 0.44–0.81)
- Cefazolin is ~80% albumin bound; 39% of patients had subtherapeutic levels

TDM and dosing

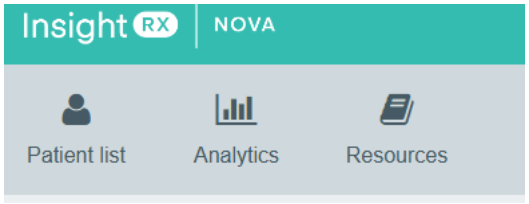
- Target 40–80 mcg/mL, but the target carries real assumptions
- Continuous infusion achieved higher levels than intermittent (61 vs 38 mcg/mL)
- Reserve TDM for patients most likely to benefit

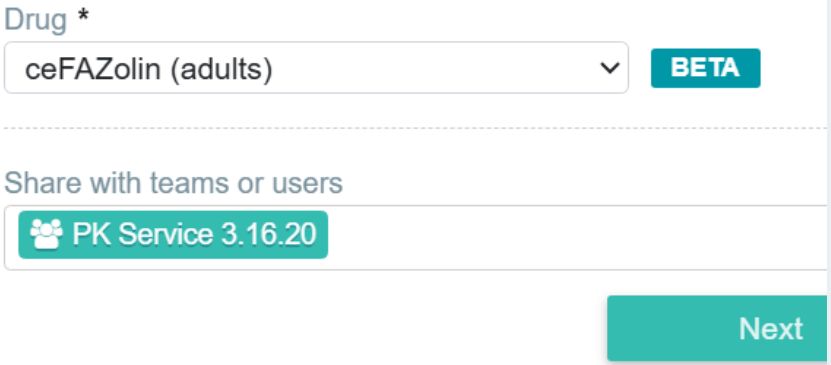
Revisiting ID Puzzle (my take)

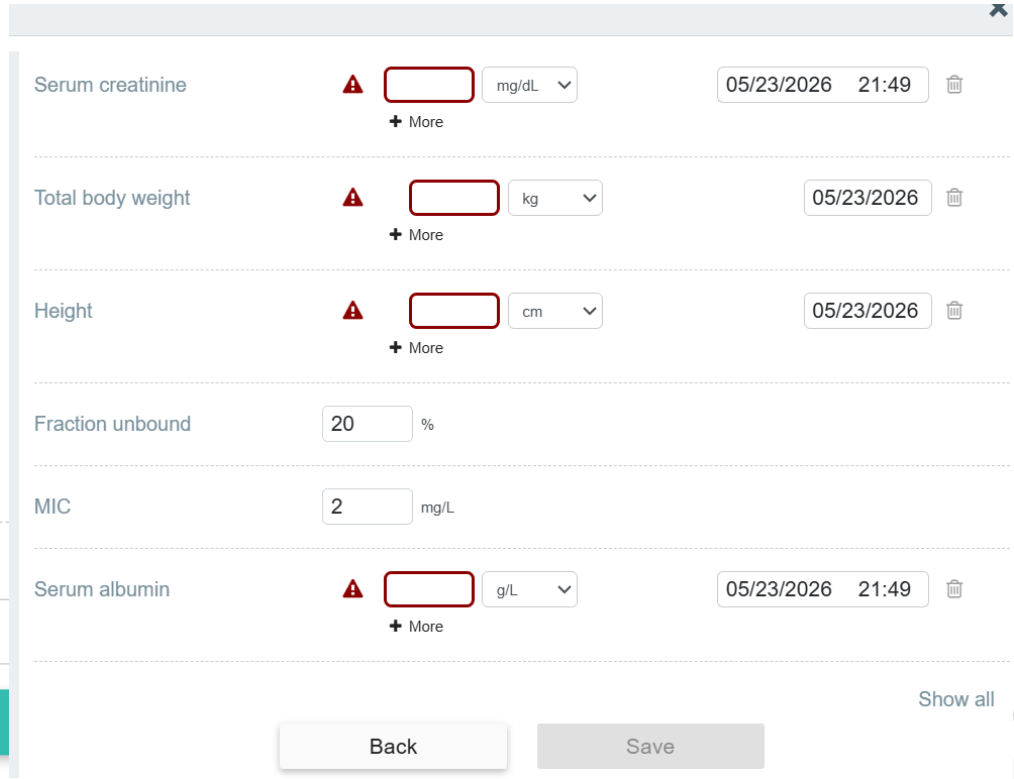


UPMC LIFE CHANGING MEDICINE

Future directions







Future directions

- How best to dose cefazolin at the time of MSSA bacteremia eplex results
  - Who should be initiated on continuous infusion (or 3h infusions) and WHEN
  - Hypoalbuminemia?
  - Combination treatment? Could incorporate into the algorithm prior to ertapenem initiation
- Validation of targets for MSSA Bacteremia
  - Ongoing experience with cefazolin TDM
  - Create standard workflows and patient identification systems
- InsightRx software for Bayesian modeling of levels
- Evaluate free concentrations (one day ☺)

Acknowledgement

Clinical Team

- **Sunish Shah**
- **Brandon Smith**
- **Ryan Shields**

- Infectious Diseases Team
- PUH AMP Team

CTSI

- Goundappa Balasubramani
- Lingyi Peng

Special thanks

- UPMC Special Chem Lab
- University Florida PK Lab
- Nicole Maranchick
- Lloyd Clarke

UPMC LIFE CHANGING MEDICINE

UPMC LIFE CHANGING MEDICINE

Low Albumin, High Stakes:

The Impact of Hypoalbuminemia Cefazolin Exposure and Blood Culture Clearance in MSSA

Rachel Marini, PharmD, BCIDP

Infectious Diseases Pharmacist

marinirv2@UPMC.edu

Slides adopted from Dr. Sunish Shah, PharmD, BCIDP