Treatment of Methicillin-Sensitive *Staphylococcus aureus*: What Does Ceftriaxone Bring to the Table?

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Financial Disclosures

No conflicts of interest to disclose

Pharmacist Learning Objectives

Compare pharmacokinetic properties and safety profiles of ceftriaxone, cefazolin, and the anti-staphylococcal penicillins

Evaluate available literature comparing ceftriaxone to cefazolin and the anti-staphylococcal penicillins for methicillin-susceptible *Staphylococcus aureus* bacteremia

Given a patient case, select the optimal antimicrobial agent between ceftriaxone or cefazolin/anti-staphylococcal penicillins for methicillin-susceptible *Staphylococcus aureus* bacteremia

Pharmacy Technician Learning Objectives

Describe the mechanisms of action of ceftriaxone and cefazolin/anti-staphylococcal penicillins for the treatment of methicillin-susceptible *Staphylococcus aureus* bacteremia

Identify the common adverse effects of ceftriaxone, cefazolin, and the anti-staphylococcal penicillins

List the differences in administration between ceftriaxone, cefazolin, and the anti-staphylococcal penicillins

Abbreviations

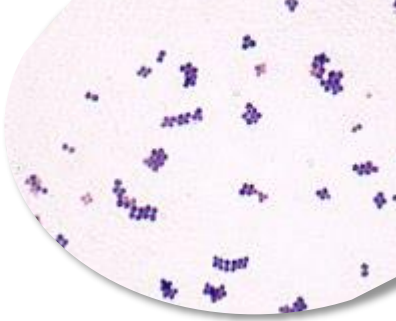
- ASP: Anti-staphylococcal penicillins (nafcillin and oxacillin)
- MSSA: Methicillin-susceptible *Staphylococcus aureus*
- TTE: Transthoracic echocardiogram
- TEE: Transesophageal echocardiogram
- OPAT: Outpatient parenteral antimicrobial therapy

Hors d'ouvres

MSSA Bacteremia

Infiltration of methicillin-sensitive
S. aureus into the bloodstream

Staphylococcus aureus



Gram-positive cocci in clusters

MSSA vs MRSA

- MRSA contains *mecA* gene which alters the penicillin-binding protein structure, prohibiting beta-lactams from binding

Sticky and virulent

- Common cause of bloodstream infections and endocarditis
- Abscess formation

Annu Rev Biochem. 2015:84:577-601

Pathophysiology

IV: Intravenous

DiPiro et al. 2024.(12).ch 134

What site of the body does Staphylococcus aureus typically colonize?

0

Mouth

0%

Gastrointestinal tract

0%

Genitourinary tract

0%

Skin

0%

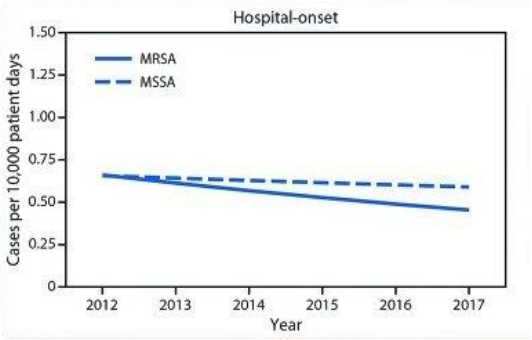
Epidemiology

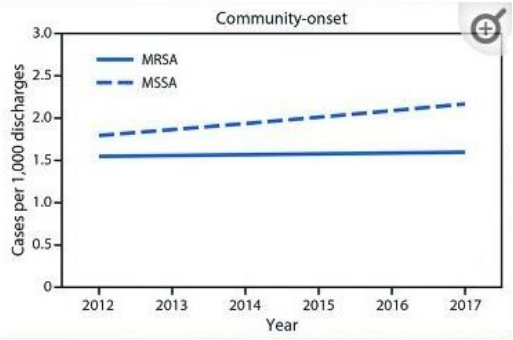
Mortality rate between 10-40%

Leading cause of infective endocarditis

- 15-40% of all cases

Hospital or community-acquired

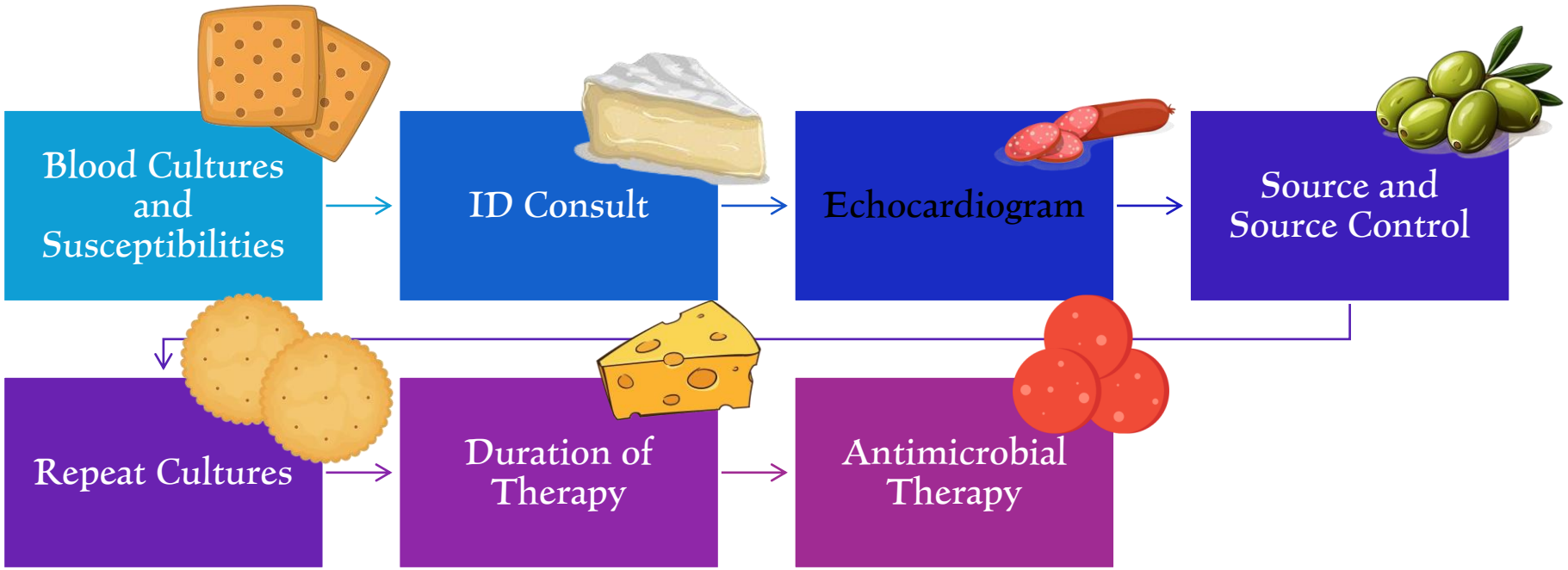




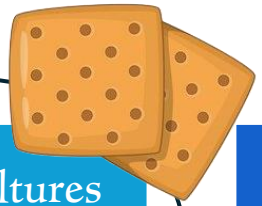
MMWR Morb Mortal Wkly Rep. 2019 Mar 8;68(9):214–219; Infect Dis (Lond). 2018 Mar;50(3):175-192; Circulation. 2020 Aug 25;142(8):720-730

Treatment of MSSA Bacteremia

MSSA Bacteremia Management



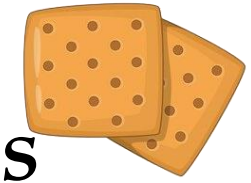
1. Blood Cultures and Susceptibilities



Blood Cultures and Susceptibilities → ID Consult → Echocardiogram → Source and Source Control

Repeat Cultures → Duration of Therapy → Antimicrobial Therapy

1. Blood Cultures and Susceptibilities



Gram stain
- Gram positive cocci in clusters

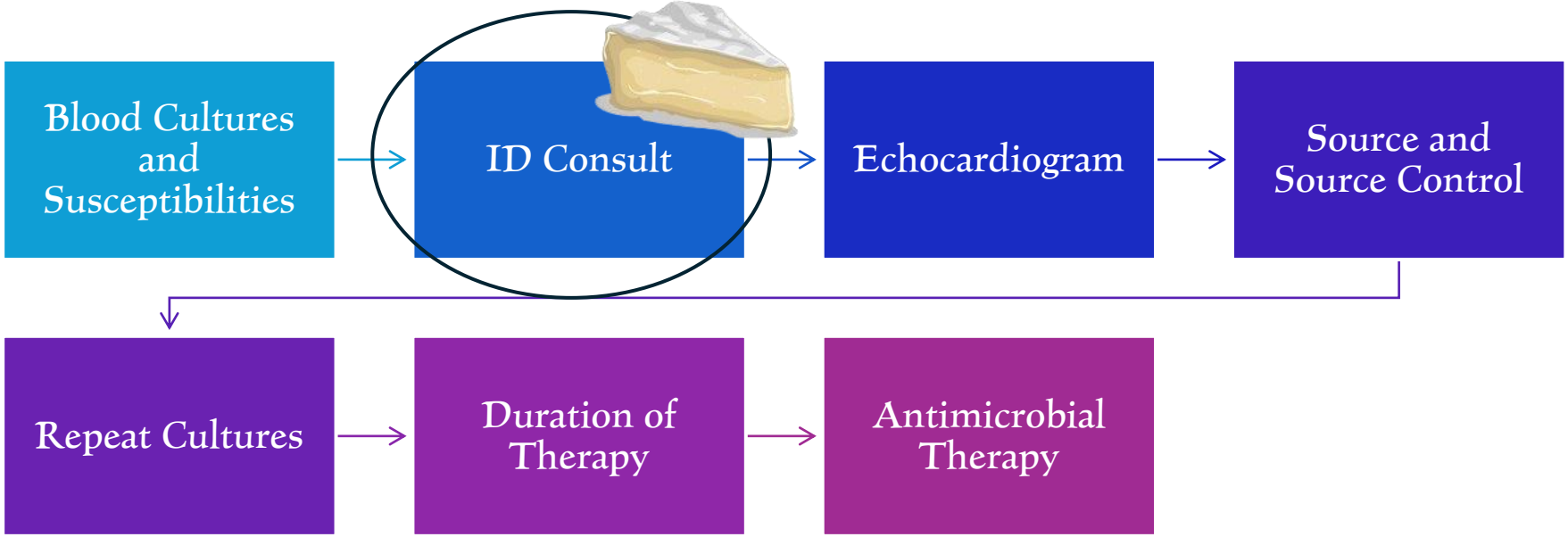
Cepheid® PCR
- *S. aureus* specific
- ~1 hour to result
- Detects *mecA* gene to differentiate between MSSA and MRSA

CLSI-Recommended Susceptibility Testing
- Macrolides
- Clindamycin
- **Oxacillin (predicts susceptibility to all beta-lactams except penicillin and aztreonam)**
- Tetracyclines
- Trimethoprim-sulfamethoxazole
- Vancomycin

CLSI: Clinical and Laboratory Standards

https://www.cepheid.com/en-US.html; CLSI M100

2. ID Consult

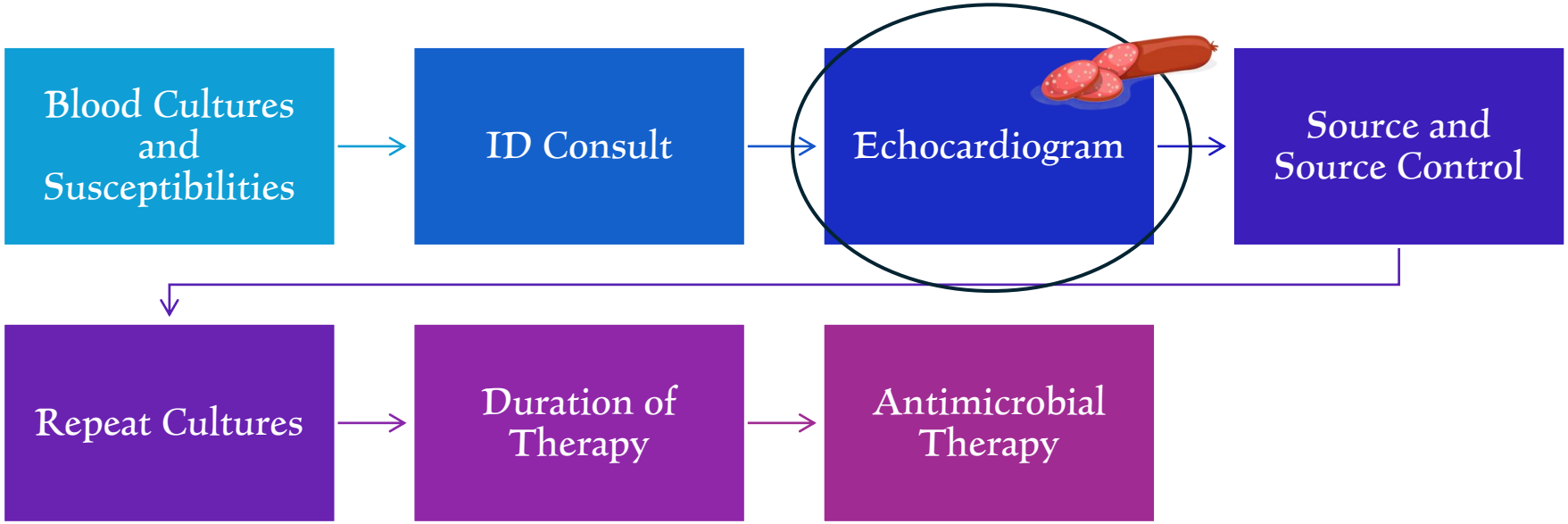

Blood Cultures and Susceptibilities
ID Consult
Echocardiogram
Source and Source Control
Repeat Cultures
Duration of Therapy
Antimicrobial Therapy

Infectious Disease (ID) Consult

An ID consult is associated with mortality benefit in the treatment of *S. aureus* bloodstream infections

JAMA Netw Open. 2020;3(2):e1921048

3. Echocardiogram



3. Echocardiogram

Use in bloodstream infections

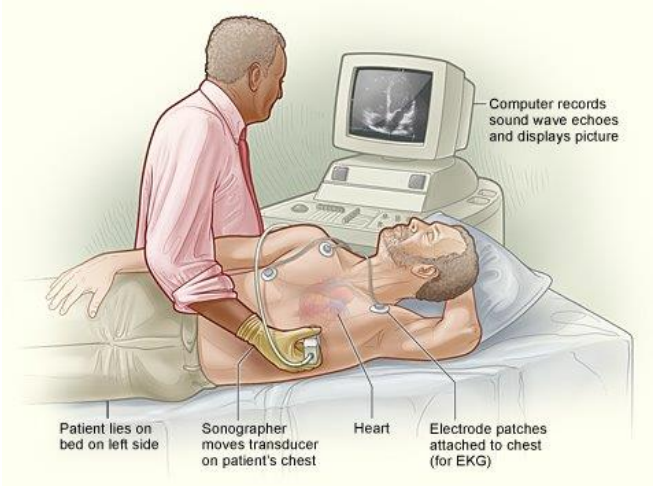
- Imaging modality used to assess for vegetations in heart valves

Techniques

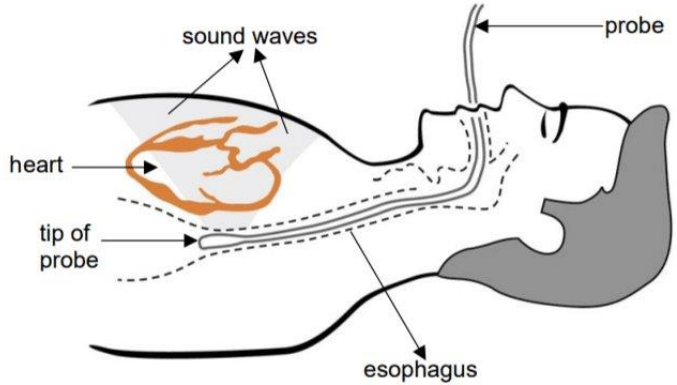
- TransThoracic Echocardiogram (TTE) → TransEsophageal Echocardiogram (TEE)

DiPiro et al, 2024.(12).ch 134

3. Echocardiogram



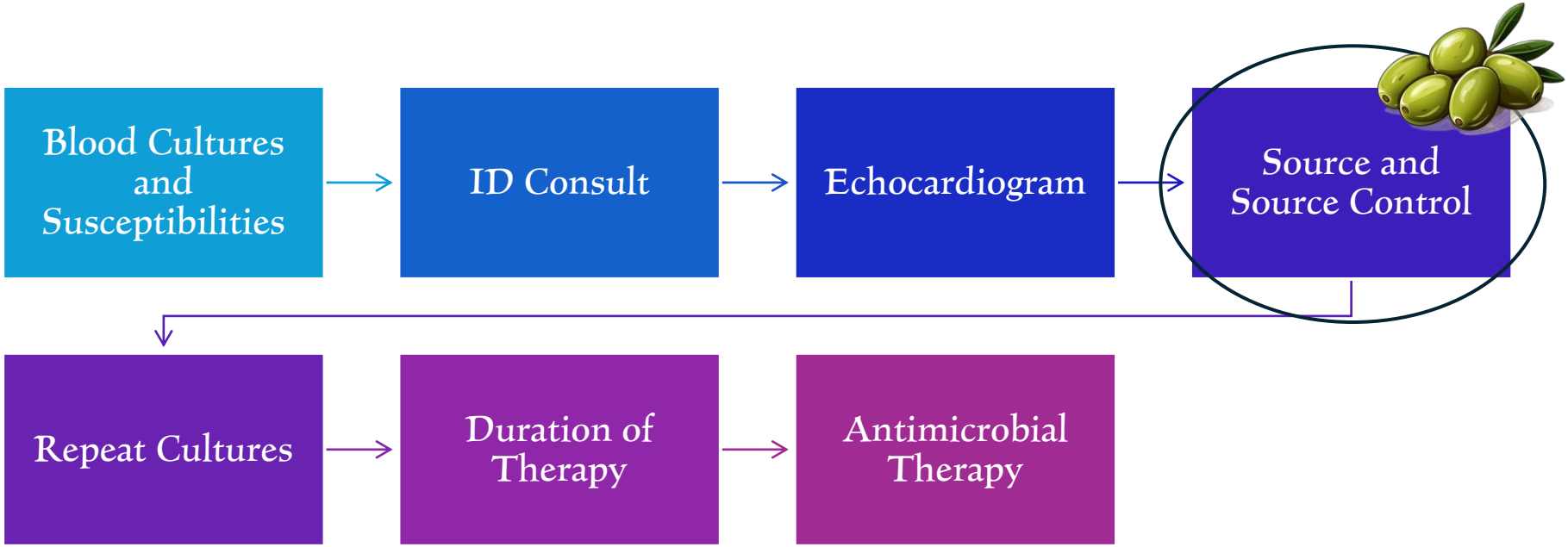
Trans-thoracic echocardiogram (TTE)



Trans-esophageal echocardiogram (TEE)

Images obtained from: http://www.nhlbi.nih.gov; https://cordoc.com/tee/;

4. Source and Source Control

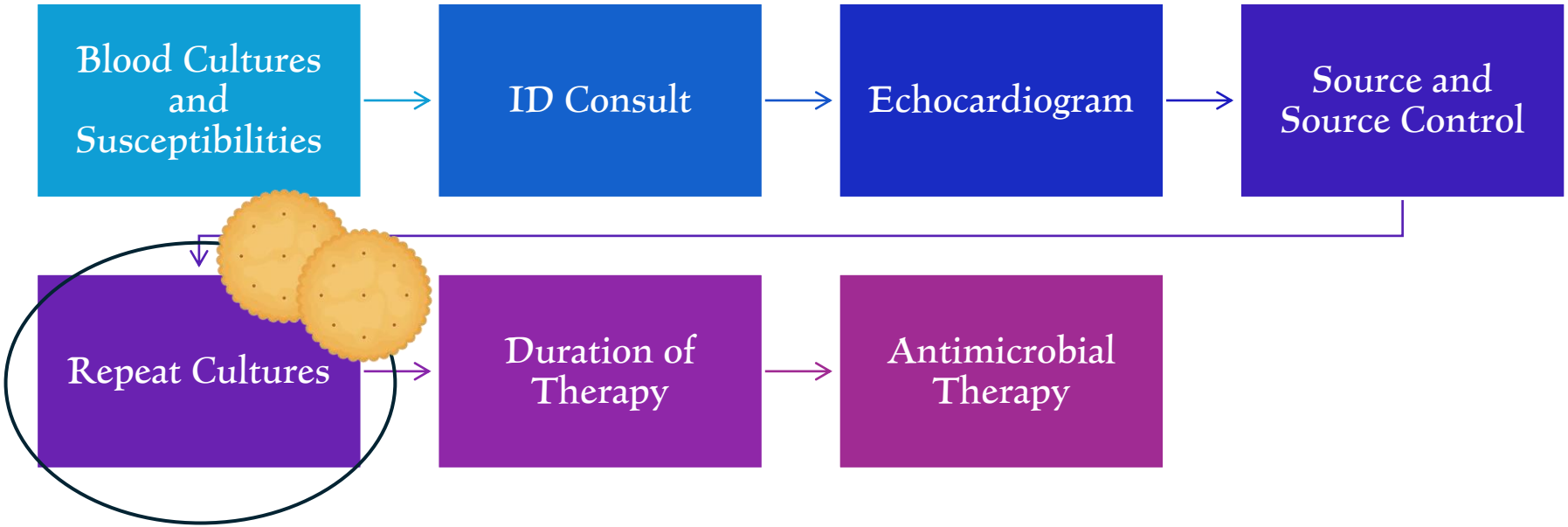


4. Source and Source Control

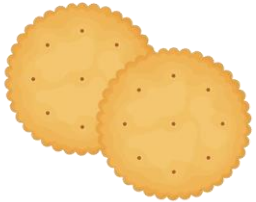
Line-associated infection	• Remove the line
Purulent skin/soft tissue infection	• Incision and drainage
Abscess	• Drain fluid collection
Endocarditis	• Surgery if: >10 mm vegetation, severe valvular insufficiency, abscess
Bone infection	• Amputation

DiPiro et al, 2024.(12).ch 134

5. Repeat Cultures



5. Repeat Cultures

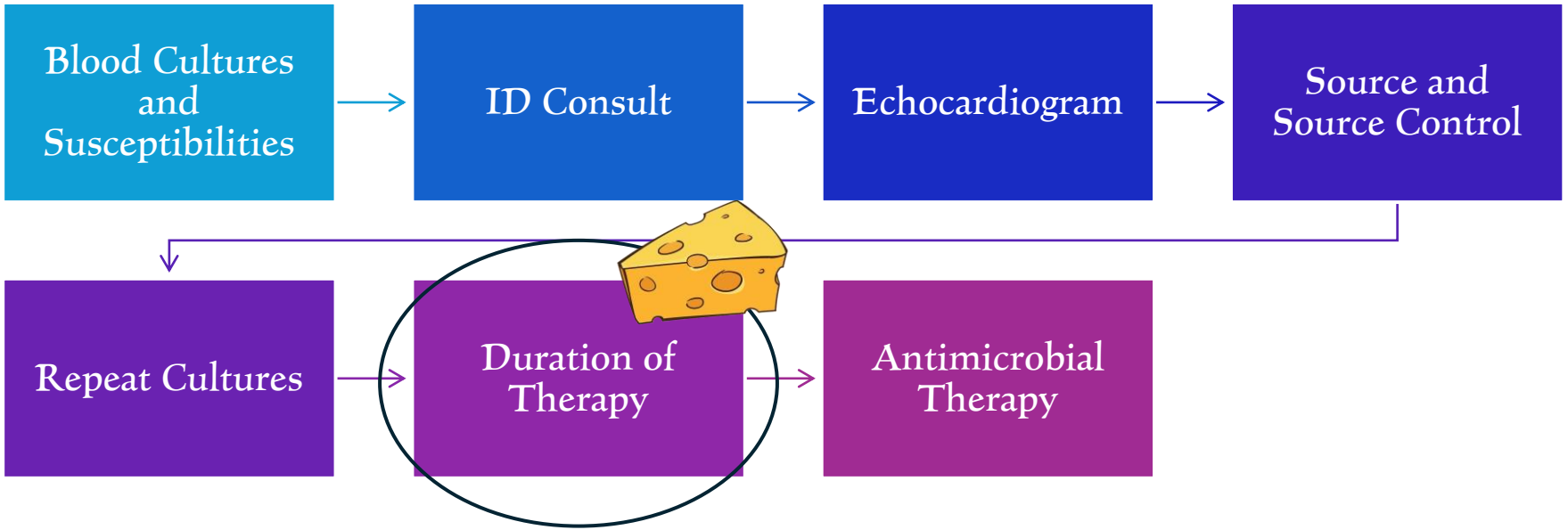


Every 24-48 hours
until blood is sterilized

Day 1 of therapy = first negative blood culture

DiPiro et al, 2024.(12).ch 134

6. Duration of Therapy



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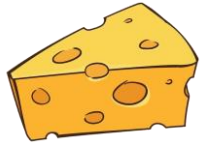


Uncomplicated	•2 weeks
Complicated	•4-6 weeks

Many patients go home on IV antibiotic therapy!

DiPiro et al, 2024.(12).ch 134

Uncomplicated *S. aureus* Bacteremia

Must meet ALL of the following criteria:

- Sterile repeat cultures within 48-96 hours
- Defervescence within 72 hours
- Exclusion of infective endocarditis
- Absence of implanted devices (e.g. heart valve, orthopedic hardware)
- Non-hemodialysis dependent

DiPiro et al, 2024.(12).ch 134

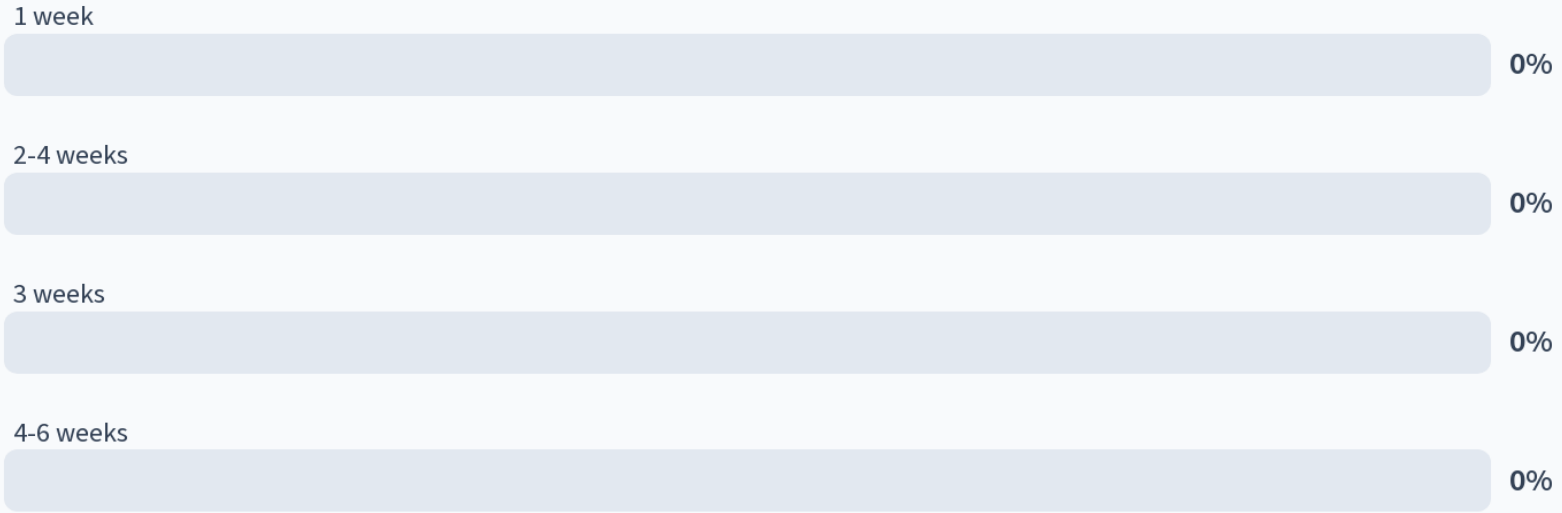
Complicated *S. aureus* Bacteremia

Must meet AT LEAST ONE of the following criteria:

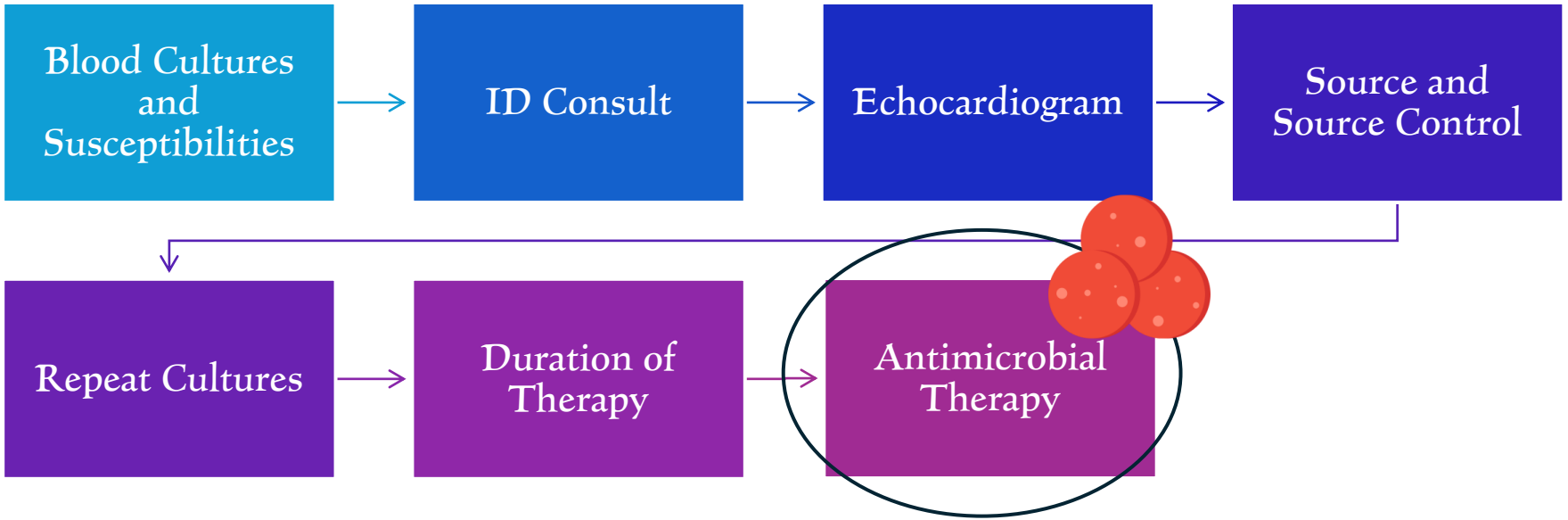
- Sterile repeat cultures within 48-96 hours
- Defervescence within 72 hours
- Exclusion of infective endocarditis
- Absence of implanted devices (e.g. heart valve, orthopedic hardware)
- Non-hemodialysis dependent

DiPiro et al, 2024.(12).ch 134

What is the duration of therapy for complicated Staphylococcus aureus bacteremia?



7. Antimicrobial Therapy



Empiric → Definitive Therapy

Using vancomycin for MSSA bacteremia is associated with a **higher mortality rate** when compared to cefazolin or the anti-staphylococcal penicillins.

Clin Infect Dis. 2015 1;61(3): 361-7

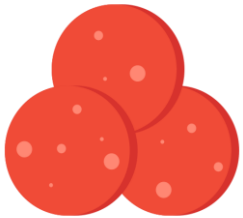
MSSA Bacteremia Treatment Options

Cefazolin

Nafcillin

Oxacillin

Ceftriaxone?



Spectrum of Activity

	MSSA	*MRSA*	*Streptococcus* spp.	*Enterococcus* spp.	*Enterobacterales*	*Pseudomonas* spp.	Anaerobes
Cefazolin	++	-	+	-	+/-	-	-
Oxacillin	++	-	+	-	-	-	-
Nafcillin	++	-	+	-	-	-	-

•Sanford Guide. (2023). Sanford guide to antimicrobial therapy (54th ed.). Antimicrobial Therapy, Inc.

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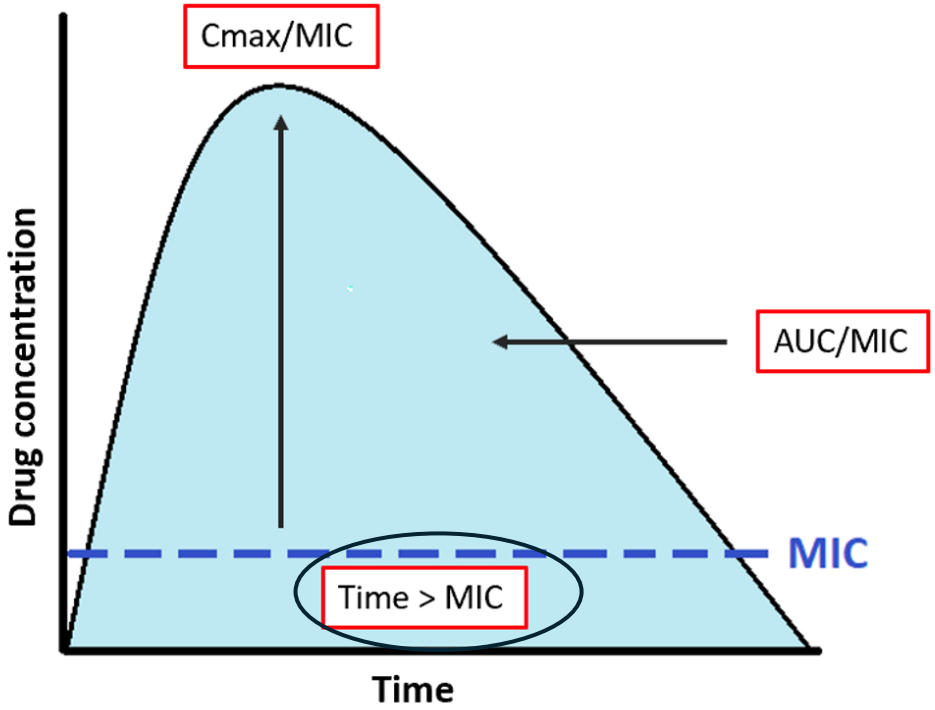
Pharmacodynamics of Beta-Lactams



Lee, S. (2021). IDStewardship.

Cefazolin, Nafcillin, and Oxacillin

Drug	Half-Life	Typical Bacteremia Dosing	Infusion Time	Renal Adjustments?	Stability at room temperature
Cefazolin	1.8 hours	2 g Q8H*	30-60 minutes or continuous infusion	Yes ESRD: 2/2/3	24 hours
Oxacillin	20-30 minutes	2 g Q4H	30 minutes or continuous infusion	No	48 hours
Nafcillin	30-60 minutes	2 g Q4H	30-60 minutes or continuous infusion	No	72 hours

*May go as high as 10 g/day in obesity or very serious infections

Cefazolin, Oxacillin, Nafcillin. *Lexi-Drugs*. UpToDate Lexidrug. UpToDate Inc

Cefazolin, Nafcillin, and Oxacillin

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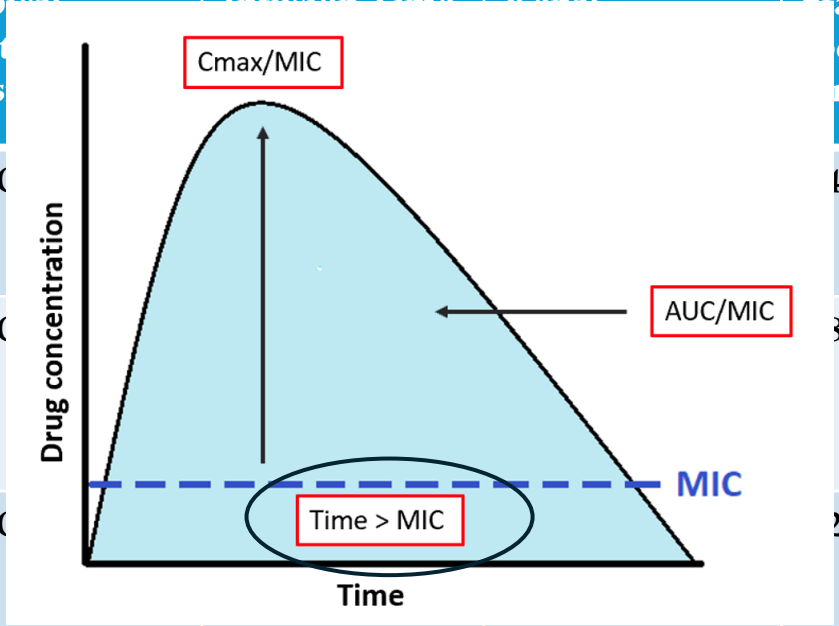
Nafcillin	30-60 minutes	2 g (			…2 hours



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Cefazolin, Oxacillin, Nafcillin. *Lexi-Drugs*. UpToDate Lexidrug. UpToDate Inc

Outpatient IV Antibiotic Adherence

Perspectives of Patients on Outpatient Parenteral Antimicrobial Therapy (OPAT): Experiences and Adherence			
Population (n=65)	Intervention	Outcome	Conclusion
Patients discharged from a tertiary hospital on OPAT between February and August 2019	Survey of patient's experience with OPAT and barriers to receiving optimal care	**Factors associated with non-adherence:** -Younger age (30 vs 64 years) -Income <$20,000 -Lack of time for administering IV antibiotics **Factors associated with adherence:** -Less frequent admin -Family or friend support	Less frequent antibiotic dosing and social support are associated with improved adherence to OPAT

Open Forum Infect Dis. 2020 Jun 2;7(6):ofaa205

Adverse Effects

Hypersensitivity reaction

Gastrointestinal

- Nausea, vomiting, diarrhea
- *C. difficile* infection

Neurologic toxicity

- Seizures

Hematologic toxicity

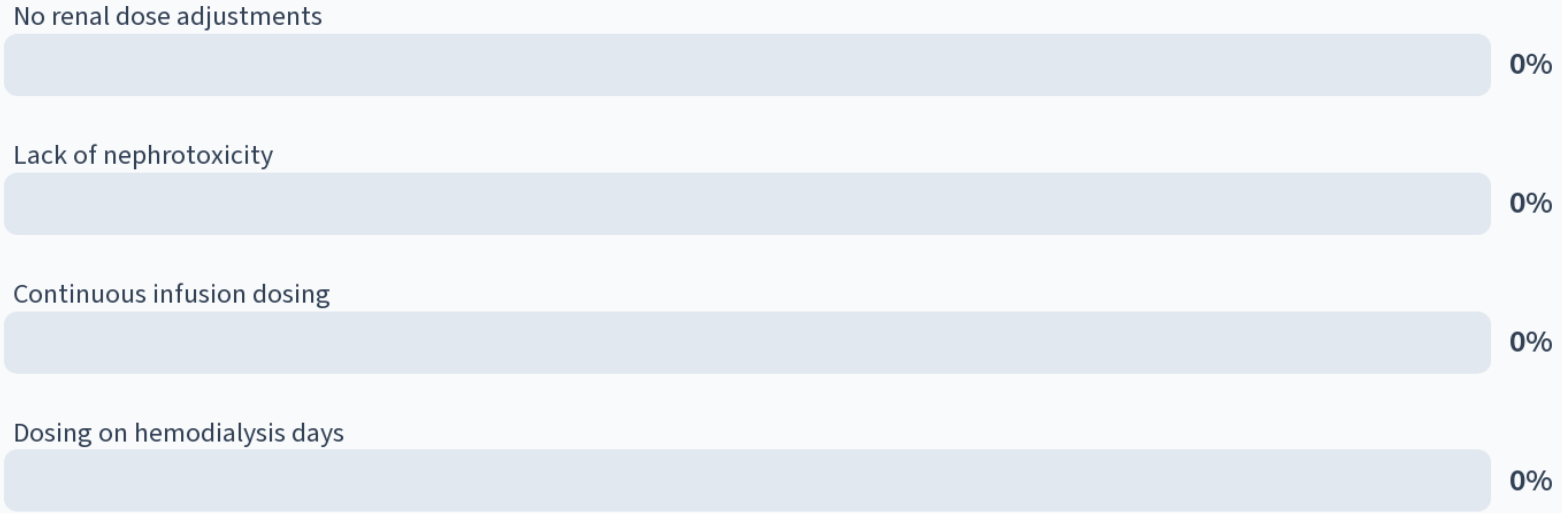
- Hemolytic anemia

Hepatotoxicity

- Oxacillin > nafcillin > cefazolin

Clin Infect Dis. 2002 Jan 1;34(1):50-4

What makes cefazolin an ideal outpatient IV antibiotic option in patients on hemodialysis?



Summary of Cefazolin/Oxacillin/Nafcillin

Pros

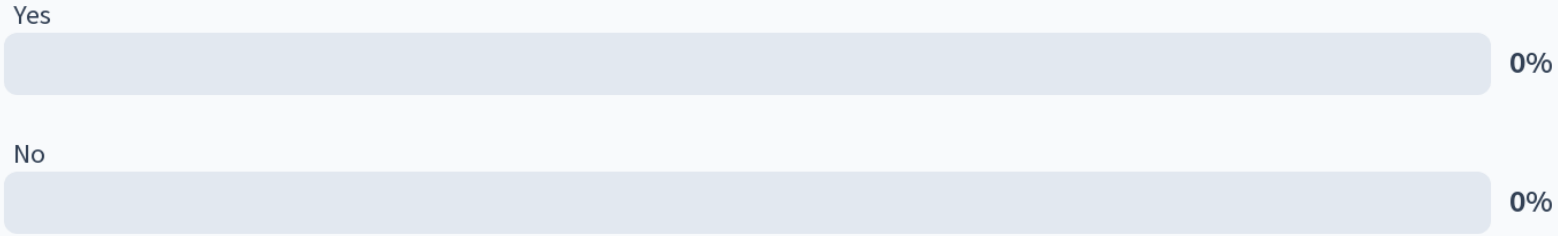
- Mortality benefit
- Cefazolin ESRD dosing
- Narrow spectrum

Cons

- Prolonged infusions
- Frequent dosing
- Hepatotoxicity with ASPs

Poll: Have you used ceftriaxone for MSSA Bacteremia?

Poll: Have you used ceftriaxone for MSSA bacteremia?



Can ceftriaxone be used to treat MSSA bacteremia?

Main dish: Turkey

Spectrum of Activity

	MSSA	MRSA	*Streptococcus* spp.	*Enterococcus* spp.	Enterobacterales	*Pseudomonas* spp.	Anaerobes
Cefazolin	++	-	+	-	+/-	-	-
Oxacillin	++	-	+	-	-	-	-
Nafcillin	++	-	+	-	-	-	-
Ceftriaxone	+	-	+	-	++	-	-

•Sanford Guide. (2023). Sanford guide to antimicrobial therapy (54th ed.). Antimicrobial Therapy, Inc.

Ceftriaxone

Drug	Half-Life	Typical Bacteremia Dosing	Infusion Time	Renal Adjustments?	Stability at room temperature
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Nafcillin	30-60 minutes	2 g Q4H	30-60 minutes or continuous infusion	No	72 hours
Ceftriaxone	5-9 hours	2g Q24H or Q12H*	IV push	No	48 hours

*2g Q12H has typically been reserved for CNS infections to achieve adequate site penetration

Ceftriaxone. Lexi-Drug. UpToDate Lexidrug. UpToDate Inc

Definitions

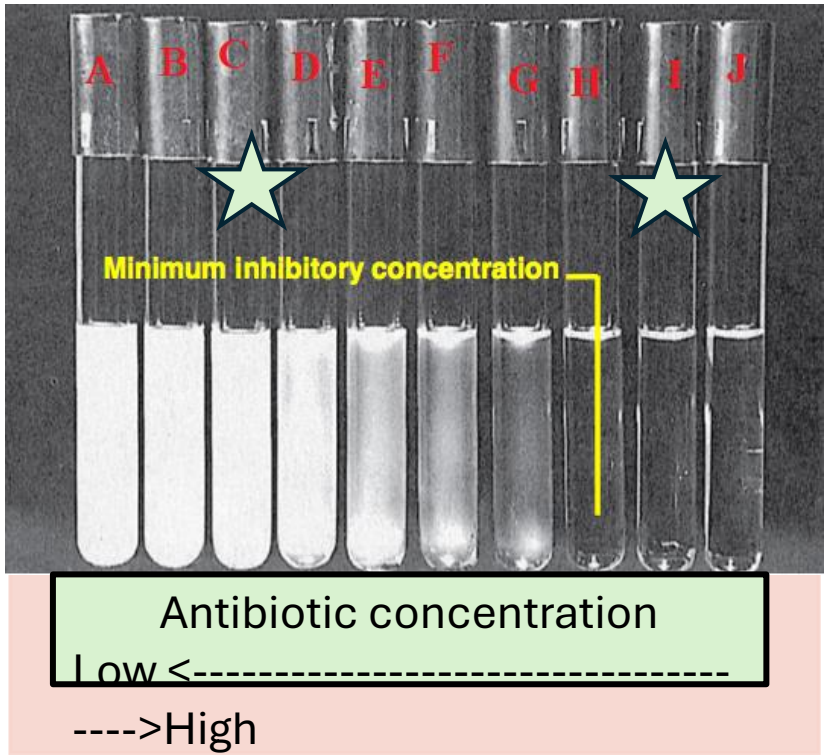


Image obtained from: micriobologyclass.net

Breakpoint

- MIC cutoff at which a bacteria is considered susceptible
- Set by CLSI

CLSI: Clinical and Laboratory

CLSI 2024 Update

Ceftriaxone breakpoint

- Oxacillin susceptibility predicts susceptibility to beta-lactams (exception: penicillin and aztreonam)

2024 CLSI Update

- Ceftriaxone IV 2 g Q12H corresponds to oxacillin breakpoint
  - Previous dosing had not been established

J Antimicrob Chemother.2018 Jul 1;73(7):1888-1894; CLSI M100

CLSI: Clinical and Laboratory

Ceftriaxone Adverse Effects

Hypersensitivity reaction

Gastrointestinal

- Nausea, vomiting, diarrhea
- *C. difficile* infection

Neurologic toxicity

- Seizures

Hematologic toxicity

- Hematolytic anemia

Hepatotoxicity

- Oxacillin > nafcillin > cefazolin/ceftriaxone

Clin Infect Dis. 2002 Jan 1;34(1):50-4; American Journal of Gastroenterology 101():p S196, September 2006.

What is the recommended dose of ceftriaxone for MSSA infections per the 2024 Clinical and Laboratory Standards Institute (CLSI) update?

Ceftriaxone 2g IV daily

0%

Ceftriaxone 1g IV every 12 hours

0%

Ceftriaxone 2g IV every 12 hours

0%

Ceftriaxone 4g IV daily

0%

Initial Ceftriaxone Data

A comparison of Cefazolin versus Ceftriaxone for the Treatment of MSSA Bacteremia in a Tertiary Care VA Medical Center, 2018

Population (n=71)	Intervention	Outcome	Conclusion
Patients with bacteremia 96% male popu Primarily oste infections			may be efazolin for t of MSSA

Treatment failure:

- Unplanned extension of parenteral antimicrobial therapy
- Failure to complete course of parenteral therapy
- Unplanned addition of suppressive oral antimicrobial therapy
- Readmission or unanticipated surgical intervention related to the primary site of infection within 90 days of treatment completion
- Patient lost to follow up

Open Forum Infect Dis. 2018 May 18;5(5):ofy089

Summary of Ceftriaxone

Pros

- IV push
- Less frequent dosing

Cons

- Unknown clinical benefit
- Higher risk of *C. difficile*

IV: Intravenous

Literature Review

Side Dishes

Literature Timeline

2020

- Hamad et al.

2023

- Yetmar et al.

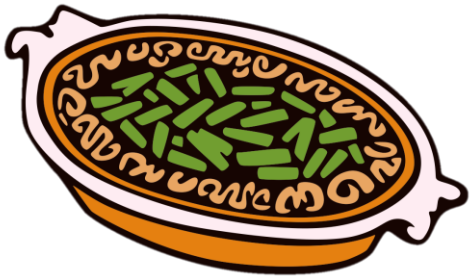
2023

- Ganguly et al.

2024

- Hamad et al

Hamad 2020



Design: single-center retrospective cohort

Inclusion Criteria

- ≥1 positive blood culture for MSSA
- Discharged on:
  - Ceftriaxone 2-4 g daily
  - Oxacillin 2g Q4H
  - Cefazolin 2 g Q8H

Exclusion Criteria

- Polymicrobial bloodstream infection
- <7 days of OPAT
- ESRD on HD

ESRD: End Stage Renal Disease
HD: Hemodialysis

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

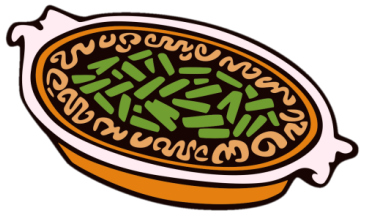
Outcomes

Primary outcome

- **<u>Treatment failure:</u>**
  - Death within 90 days of discharge
  - Readmission related to MSSA infection within 90 days
  - Microbiologic failure within 90 days (subsequent isolation of MSSA from a sterile site)

Secondary outcomes

- Microbiologic failure
- 90-day all-cause mortality
- Readmission due to MSSA infection within 90 days
- Change in antibiotics due to toxicity after discharge



Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Baseline Characteristics

Characteristic, No. (%) or Median (IQR)	Oxacillin/ cefazolin (n=95)	Ceftriaxone (n=148)	P-value
Age, y	57.1 (46.4-68.2)	61.3 (48.9-71.5)	0.08
BMI	29.1 (23.5-35.6)	27.3 (23.5-33.3)	0.84
ICU stay	46 (48.8)	43 (29.1)	<0.01
TTE	86 (90.5)	142 (95.5)	0.09
TEE	56 (59)	37 (25)	<0.01
Total duration of therapy, d	42 (42-44)	42 (28-43)	0.01
PO antibiotic suppression	25 (26)	19 (13)	<0.01
Source control not achieved	9 (9.5)	14 (9.5)	0.99

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Source of Infection

Source of Infection, no (%)	Oxacillin/ cefazolin (n=95)	Ceftriaxone (n=148)	P-value
Primary bacteremia	13 (13.7)	27 (18.2)	0.35
Central-line associated	22 (23.2)	48 (32.4)	0.12
Prosthetic material	11 (11.6)	15 (10.1)	0.72
Skin/soft tissue	9 (9.5)	24 (16.2)	0.13
Surgical site	3 (3.2)	13 (8.8)	0.05
Osteomyelitis	20 (21.1)	20 (13.5)	0.12
Septic arthritis/ PJI	12 (12.6)	16 (10.8)	0.66
Epidural abscess	6 (6.3)	7 (4.7)	0.59
Endocarditis	41 (43.2)	42 (28.4)	0.02

PJI: prosthetic joint infection
Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Results

Endpoint, no (%)	Oxacillin-cefazolin (n=95)	Ceftriaxone (n=148)	P-value
Composite primary outcome	18 (19)	31 (21)	0.70
Microbiologic failure	6 (6.3)	9 (6.1)	0.94
90-day all-cause mortality	7 (7.4)	15 (10.1)	0.46
Readmission due to MSSA infection	10 (10.5)	13 (8.8)	0.65
Change in antibiotics due to toxicity	4 (4.2)	6 (4.1)	0.95

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Endocarditis Subgroup

Endpoint, no (%)	Oxacillin-cefazolin (n=41)	Ceftriaxone (n=42)	P-value
Composite primary outcome	4 (10)	11 (25.6)	0.17
Microbiologic failure	3 (7.3)	3 (7.1)	0.99
90-day all-cause mortality	1 (1.4)	6 (14.3)	0.11
Readmission due to MSSA infection	3 (7.3)	3 (7.1)	0.99
Change in antibiotics due to toxicity	0 (0)	1 (2.4)	0.99

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Multivariate Analysis

	Risk of Treatment Failure		
Variable	**Hazard Ratio**	**95% CI**	**P-value**
Age >65 y	0.907	0.484 – 1.700	0.76
Endocarditis	0.884	0.471 – 1.660	0.70
Lack of source control	1.080	0.426 – 2.737	0.87
Discharged on ceftriaxone	0.994	0.537 – 1.841	0.99
Discharge to post-acute care facility	1.769	0.974 – 3.214	0.06

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Critique

Strengths

- Multivariate analysis
- Cost analysis
- Dosing clarity
- Endocarditis subgroup

Limitations

- Did not meet power
- Patients sicker in the cefazolin/oxacillin group
- No analysis of ID consultations

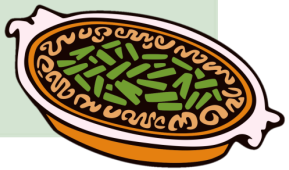
Conclusions

Author's Conclusions

- Use of ceftriaxone was not associated with increased risk of treatment failure. However, this study did not meet power, therefore interpret results with caution

My Conclusions

- This data is insufficent to confirm that ceftriaxone is an effective treatment option for MSSA bacteremia



Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341

Yetmar 2023

Design: **multi**-center retrospective cohort

Inclusion Criteria

- MSSA bacteremia
- ≥18 years old
- ≥7 days outpatient treatment with ceftriaxone, cefazolin, or an ASP
- Follow up at least through the end of treatment

Exclusion Criteria

- < 7 days outpatient treatment
- Polymicrobial bacteremia
- Definitive treatment with antibiotics other than cefazolin, ceftriaxone, or an ASP
- Outpatient combination therapy
- Chronic suppressive antibiotic therapy following definitive course
- Lack of research authorization per Minnesota statute

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Outcomes

Primary outcome

- 90-day treatment failure
  - Composite of mortality and microbiologic recurrence (isolation of *S. aureus* in the setting of a compatible clinical syndrome)

Secondary outcomes

- 30-day treatment failure
- 30- day mortality
- Microbiological recurrence in 30 and 90-days

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Baseline Characteristics

Characteristic, No. (%) or Mean (SD)	ASP or cefazolin (n=186)	Ceftriaxone (n=37)
Age, y	62.1 (16.9)	68.2 (15.8)
BMI	30.3 (8.1)	30.4 (7.9)
ID Consult	183 (98.4)	34 (91.9)
Source Control	183 (98.4)	37 (100)
TEE Performed	110 (59.1)	15 (40.5)
Complicated bacteremia	134 (72)	20 (54.1)
Total antibiotic duration, days, median, IQR	32 (27.2, 45)	28 (**16**, 45)
Infective endocarditis	24 (12.9)	2 (5.4)

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Source of Infection

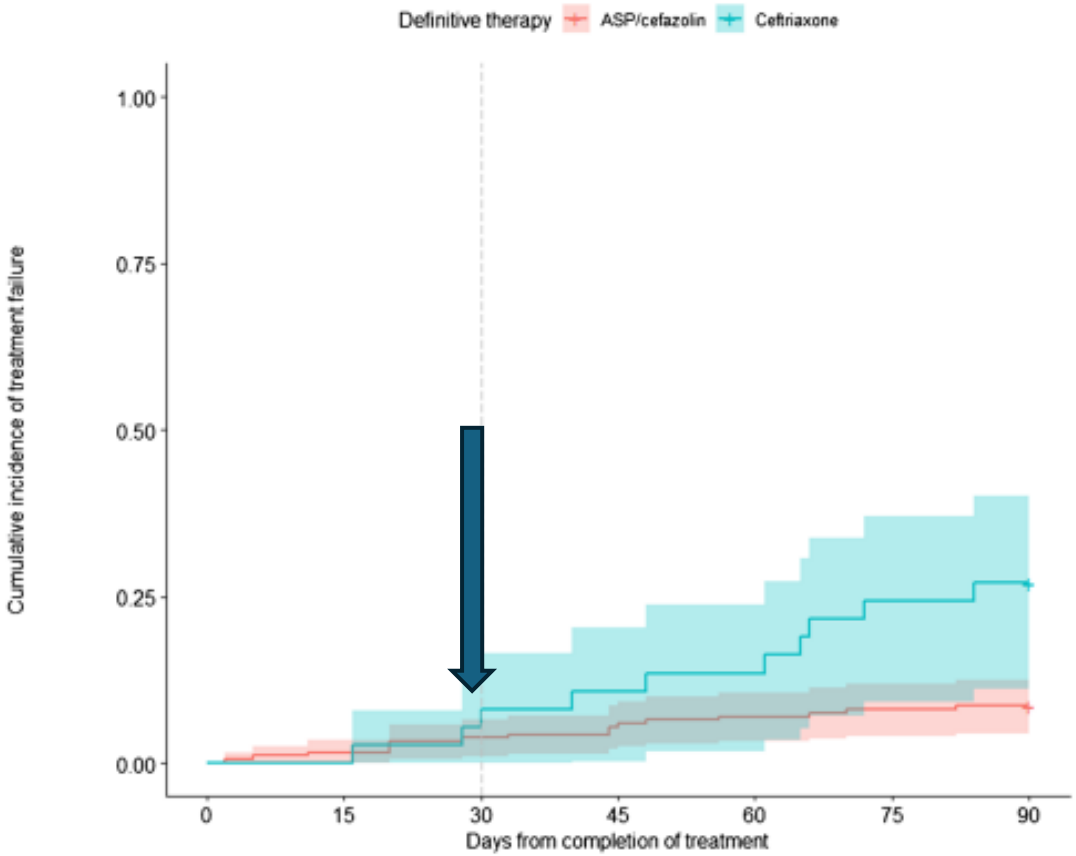
Source of Infection, no (%)	ASP or cefazolin (n=186)	Ceftriaxone (n=37)
Catheter-related	31 (16.7)	3 (8.1)
Infective endocarditis	1 (0.5)	0 (0)
Gastrointestinal	3 (1.6)	2 (5.4)
Genitourinary	7 (3.8)	1 (2.7)
Osteoarticular	21 (11.3)	4 (10.8)
Pneumonia	9 (4.8)	4 (10.8)
Skin/soft tissue	67 (36)	16 (43.2)
Unknown	42 (22.6)	5 (13.5)
Other	5 (2.7)	2 (5.4)

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Results

Endpoint, no (%)	ASP or cefazolin (n=186)	Ceftriaxone (n=37)
90-day treatment failure	16 (8.6)	10 (27)
- 90-day mortality	11 (5.9)	7 (18.9)
- 90-day recurrence	5 (2.7)	3 (8.1)
30-day treatment failure	7 (3.8)	3 (8.1)
- 30-day mortality	4 (2.2)	2 (5.4)
- 30-day recurrence	3 (1.6)	1 (2.7)

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430



Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Risk of 90-day Treatment Failure

Variable	Hazard Ratio (95% confidence interval)	P-value
Ceftriaxone	1.66 (1.15 – 6.12)	0.022
Age-adjusted Charleston Comorbidity Index	1.10 (1.10 – 1.20)	0.033
Total antibiotic duration (per day)	0.96 (0.93 – 0.99)	0.014
TEE performed	0.94 (0.38 – 2.31)	0.886

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Critique

Strengths

- Objective end points
- 30 and 90-day mortality
- Obese population

Limitations

- Limited dosing information
- 90-day endpoints
- Lack of endocarditis patients in ceftriaxone group

Conclusions

Author's Conclusions

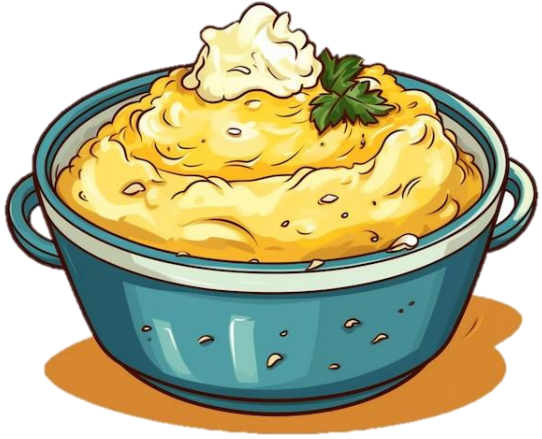
- Use of ceftriaxone was associated with similar 30-day mortality and higher 90-day mortality and treatment failure when compared to cefazolin/ASPs

My Conclusions

- A similar 30-day mortality indicates that ceftriaxone may be a viable option for MSSA bacteremia

Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430

Ganguly 2023



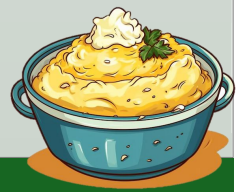
Design: single-center retrospective cohort

Inclusion Criteria

- Diagnosed with MSSA bacteremia
- Either
  - Ceftriaxone 2g Q24H
  - Cefazolin 2 g Q8H (with renal dose-adjustments)
- S-OPAT group

Exclusion Criteria

- Not explicitly defined

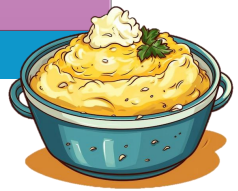


S-OPAT: Self-administered

Ann Pharmacother. 2023 Apr;57(4):425-431.

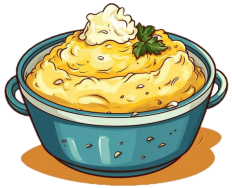
S-OPAT

Self-administered Outpatient Parenteral Antimicrobial Therapy		
Patient/caregiver trained by nursing staff to self-administer IV antibiotics (via gravity or IV push)	4th-grade literacy level and "teach-back method" used for patient comprehension	Education on care of IV access catheter and weekly laboratory monitoring



Ann Pharmacother. 2023 Apr;57(4):425-431.

Outcomes



Primary outcome

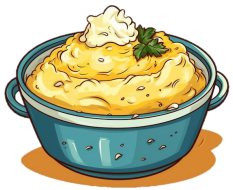
- Composite:
  - Repeat positive blood cultures
  - Retreatment within 6 months of completing the prescribed treatment course

Secondary outcomes

- 30-day all-cause hospital readmission rates
- Central-line-associated bloodstream infection (CLABSI) rates
- Rates of adverse drug events

Ann Pharmacother. 2023 Apr;57(4):425-431.

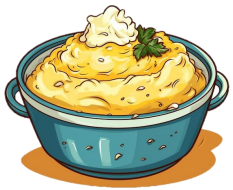
Baseline Characteristics



Characteristic	Cefazolin (n=222)	Ceftriaxone (n=82)	P-value
Age, y. mean +/- SD	50 +/- 14	50 +/- 11	0.74
Duration of therapy, d, mean +/- SD	34 +/- 17	35 +/- 18	0.65
Hispanic, no (%)	142 (50)	50 (61)	-

Ann Pharmacother. 2023 Apr;57(4):425-431.

Source of Infection



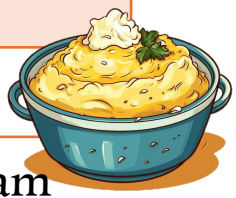
Source of Infection, no (%)	Cefazolin (n=222)	Ceftriaxone (n=82)	P-value
Bone and joint	84 (29)	44 (54)	<0.01
Bacteremia	39 (14)	7 (9)	
CLABSI	33 (12)	2 (2)	
Endocarditis	54 (19)	7 (9)	
Genitourinary	13 (5)	5 (6)	
Skin/soft tissue	48 (17)	15 (18)	
Other	2 (1)	0 (0)	

CLABSI: Central-line-associated bloodstream infection

Ann Pharmacother. 2023 Apr;57(4):425-431.

Results

Endpoint, no (%)	Cefazolin (n=222)	Ceftriaxone (n=82)	P-value
Treatment failure, no (%)	10 (4)	2 (2)	1.00
Re-treatment with IV antibiotic therapy	7 (2.4)	2 (2.4)	
Repeat positive blood cultures	4 (1.4)	0 (0)	
30-day all cause readmission rate, no (%)	62 (22)	17 (21)	0.85
CLABSI rate, no (%)	31 (11)	2 (2)	0.02
Adverse events, no (%)			
C. difficile infection	8 (2.8)	2 (2.4)	
Drug rash	0 (0)	1 (0.35%)	



Ann Pharmacother. 2023 Apr;57(4):425-431.

CLABSI: Central-line-associated bloodstream

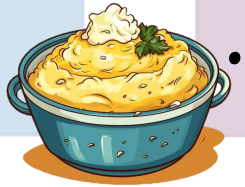
Critique

Strengths

- Met power with larger sample size
- Dosing included
- Objective outcomes
- Great patient support

Limitations

- Low external validity
- No analysis of ID consults, echocardiograms, source control, or ICU stays
- No analysis of mortality
- No exclusion criteria



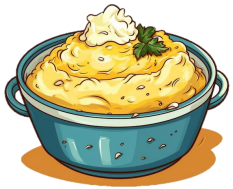
Conclusions

Author's Conclusions

- Ceftriaxone was non-inferior to cefazolin in the S-OPAT setting, particularly in bone, joint, and skin/soft tissue sources of infections

My Conclusions

- Ceftriaxone was a viable option for MSSA bacteremia in the S-OPAT setting however, this data is not generalizable



Ann Pharmacother. 2023 Apr;57(4):425-431.

Hamad 2024

Design: retrospective cohort

Inclusion Criteria

- 18-64 years old
- Hospitalization coded with ICD-9/10-CM codes for MSSA septicemia
- Prescription for cefazolin, ceftriaxone, oxacillin, or nafcillin for home or outpatient infusion within 7 days of hospital discharge
- Medical coverage for 1 year prior to index hospitalization

Exclusion Criteria

- >65 and ESRD (Medicare conflicts)
- Discharged to skilled nursing facility
- Use of other antibiotics with anti-staphylococcal activity within 7 days of discharge

ESRD: End Stage Renal Disease

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Primary outcomes

- Readmission to a hospital with the same infectious category as the index admission within 90 days
- All-cause readmission within 90-days

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Baseline Characteristics

Characteristic, no (%)	ASP or cefazolin (n=1535)	Ceftriaxone (n=460)	P-value
Age, y. median, IQR	50.7 (54-60)	50.9 (46-60)	0.157
Urban residence	1229 (88.1)	386 (86.1)	0.282
ICU stay	727 (50.6)	230 (50)	0.804
ID consultation	1013 (70.5)	295 (64.2)	0.009
Echocardiography completed	1036 (72.2)	270 (54.6)	<0.001
OPAT duration, d, median (IQR)	15 (7-29)	15 (8-29)	0.076

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Source of Infection

Source of Infection, no (%)	ASP or cefazolin (n=1535)	Ceftriaxone (n=460)	P-value
Osteomyelitis	260 (18.2)	75 (16.3)	0.375
Septic arthritis	198 (13.8)	53 (11.5)	0.210
PJI	129 (6.8)	33 (7.1)	0.220
CLABSI	137 (7.2)	38 (8.2)	0.407
Vascular device	156 (10.8)	36 (7.8)	0.596
Skin/soft tissue	587 (40.1)	170 (36.9)	0.132
Surgical site	437 (30.4)	121 (26.3)	0.099
Epidural abscess	170 (11.9)	30 (6.5)	0.002
Endocarditis	229 (15.9)	47 (10.2)	0.002
Pneumonia	255 (17.7)	101 (22)	0.045

PJI: prosthetic joint infection
CLABSI: central-line associated bloodstream infection
Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Factors Associated with Readmission

	Readmission with Same Infection			
Variable, no (%)	**Yes (n=366)**	**No (n=1529)**	**P-value**	**aOR (95% CI)**
Obesity	113 (30.9)	369 (24.1)	0.011	1.40 (1.07-1.82)
ICU stay	245 (66.9)	712 (46.6)	<0.001	2.33 (1.81-3.01)
Central-line associated bloodstream infection	48 (13.1)	127 (8.3)	0.001	1.72 (1.33-2.94)
Prosthetic joint infection	43 (11.8)	119 (7.8)	0.001	1.96 (1.25-2.23)
Endocarditis	71 (19.4)	205 (13.4)	0.002	1.63 (1.18-2.23)
Ceftriaxone	78 (21.3)	382 (25)	0.428	0.89 (0.67-1.18)

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Factors Associated with Readmission

All Readmissions				
Variable, no (%)	**Yes (n=535)**	**No (n=1360)**	**P-value**	**aOR (95% CI)**
Obesity	153 (28.6)	329 (24.1)	0.052	1.23 (0.99-1.61)
ICU stay	355 (66.4)	602 (44.2)	<0.001	2.42 (1.92-3.02)
Central-line associated bloodstream infection	76 (14.2)	99 (7.2)	<0.001	2.48 (1.76-3.49)
Prosthetic joint infection	56 (10.4)	106 (7.8)	0.003	1.74 (1.19-2.53)
Endocarditis	100 (18.6)	176 (12.9)	0.001	1.60 (1.22-2.14)
Ceftriaxone	114 (21.3)	346 (25.4)	0.230	0.86 (0.66-1.10)

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Antibiotic Choice and Risk of Readmission

	Readmission with Same Infection			All Readmissions		
Variable, no (%)	**Yes (n=366)**	**No (n=1529)**	**P-value**	**Yes (n=535)**	**No (n=1360)**	**P-value**
Ceftriaxone, propensity score-weighting	78 (21.3)	382 (25)	0.937	114 (21.3)	346 (25.4)	0.203

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Endocarditis Subgroup

Endpoint, no (%)	Oxacillin/ Nafcillin/ Cefazolin (n=229)	Ceftriaxone (n=47)	P-value
90-day All-Cause Readmission	85 (37.1)	15 (31.9)	0.499
Readmitted with the same infection category	62 (27.1)	9 (19.1)	0.257

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Critique

Strengths

- Large study size
- ICU stays matched
- Inverse propensity weighting

Limitations

- Dosing not included
- Insurance database is limiting
- 90-day analysis
- No mortality assessment

Conclusions

Author's Conclusions

- Ceftriaxone use for MSSA bacteremia was not associated with a higher risk for readmission

My Conclusions

- Similar readmission rates indicates efficacy may be comparable, however lack of mortality data presents a challenge to implementation of ceftriaxone for MSSA bacteremia

Open Forum Infect Dis. 2024 Jan 12;11(2):ofad662

Summary of the Data

Mixed mortality data

- Most studies evaluated 90-days

Readmission rates were not different

Major lack of endocarditis patients in the ceftriaxone groups

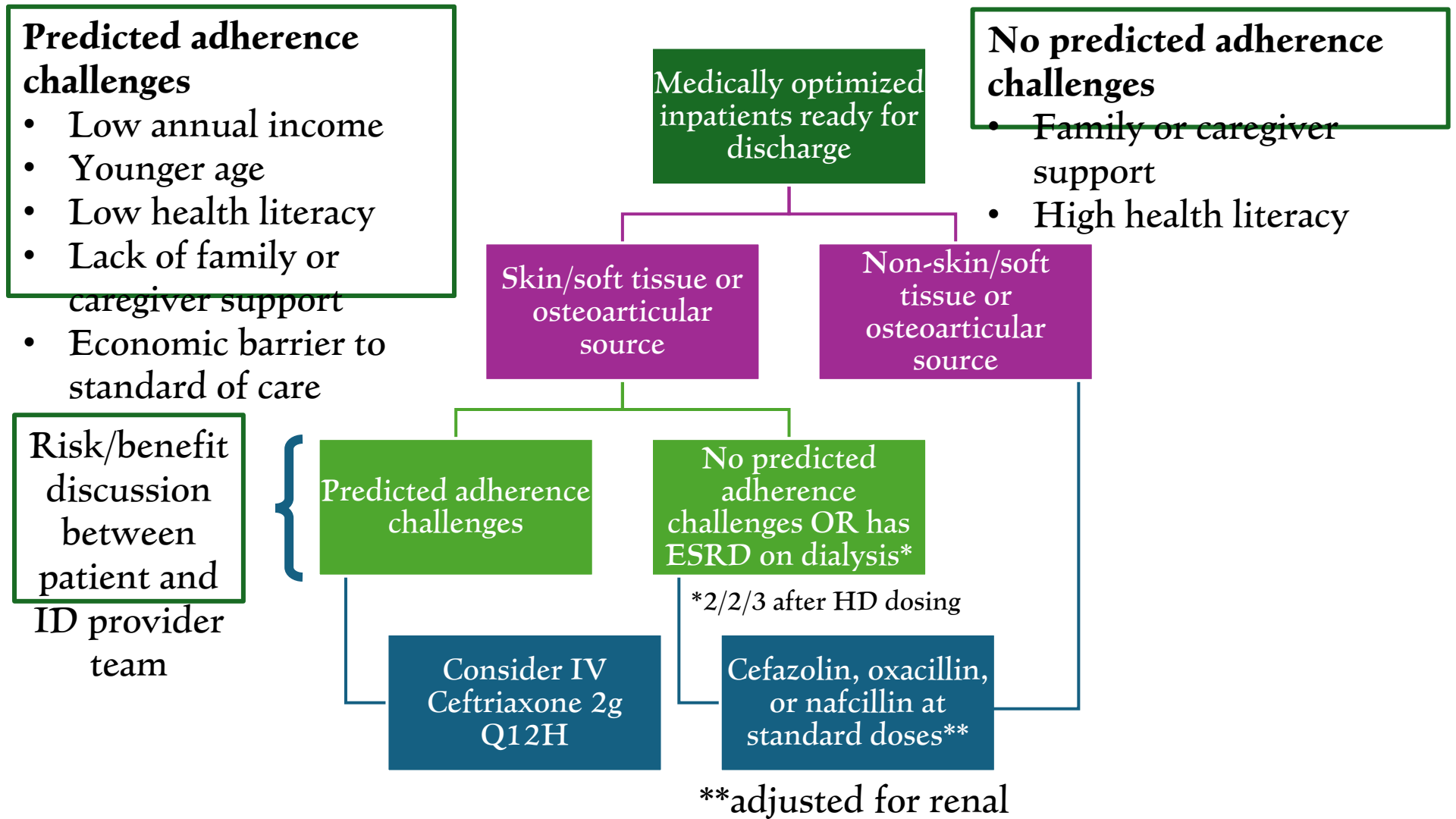
Dosing??

Algorithm

Time for dessert!

Pre-Discharge Checklist

- ID consult completed
- Clear blood cultures
- Adequate source-control as deemed by ID physician
- Clinically stable
  - No longer meeting SIRS criteria


Predicted adherence challenges
• Low annual income
• Younger age
• Low health literacy
• Lack of family or caregiver support
• Economic barrier to standard of care
No predicted adherence challenges
• Family or caregiver support
• High health literacy
Medically optimized inpatients ready for discharge
Skin/soft tissue or osteoarticular source
Non-skin/soft tissue or osteoarticular source
Risk/benefit discussion between patient and ID provider team
Predicted adherence challenges
No predicted adherence challenges OR has ESRD on dialysis*
*2/2/3 after HD dosing
Consider IV Ceftriaxone 2g Q12H
Cefazolin, oxacillin, or nafcillin at standard doses**
**adjusted for renal

Future Directions

- Comparison of ceftriaxone 2g Q12H to standards of care
- More robust 30-day mortality
- Endocarditis outcomes
- Delineation of complicated and uncomplicated infections

Resources for Pharmacists

1. CLSI. Performance Standards for Antimicrobial Susceptibility Testing. 34th ed. CLSI Standard M100. Clinical Laboratory Standards Institute; 2024.
2. Yetmar ZA, Khodadadi RB, Go JR, Chesdachai S, Abu Saleh OM. Post-treatment outcomes of ceftriaxone versus antistaphylococcal penicillins or cefazolin for definitive therapy of methicillin-susceptible Staphylococcus aureus bacteremia. Eur J Clin Microbiol Infect Dis. 2023 Apr;42(4):423-430. doi: 10.1007/s10096-023-04575-z. Epub 2023 Feb 17. PMID: 36800065.
3. Yasir Hamad, Katelin B Nickel, Margaret A Olsen, Ige A George, Outcomes of Ceftriaxone Compared With Cefazolin or Nafcillin/Oxacillin for Outpatient Therapy for Methicillin-Sensitive Staphylococcus aureus Bloodstream Infections: Results From a Large United States Claims Database, Open Forum Infectious Diseases, Volume 11, Issue 2, February 2024, ofad662, https://doi.org/10.1093/ofid/ofad662

Post-Test Questions

What is a potential advantage of using ceftriaxone over cefazolin or the anti-staphylococcal penicillins?

Ceftriaxone has a long half-life that allows for more infrequent dosing

0%

Ceftriaxone is less likely to cause C. difficile infections

0%

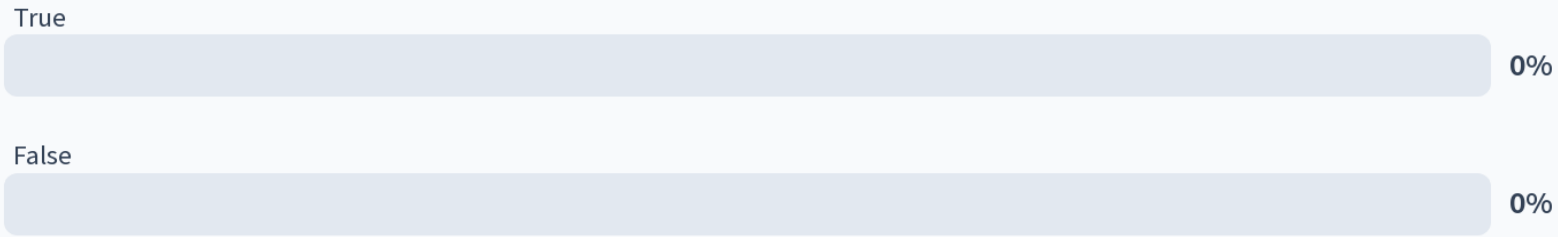
Ceftriaxone is offered as a continuous infusion, which is easier than multi-dose per day dosing

0%

Ceftriaxone can be dosed three-times weekly on dialysis days

0%

True or False? In the Yetmar et al. study from 2023, 30-day mortality was similar between the cefazolin and anti-staphylococcal penicillin group and the ceftriaxone group, but 90-day mortality was higher in the ceftriaxone group.



3. A patient on your ID consult service with MSSA bacteremia secondary to endocarditis is preparing for discharge. The patient is medically optimized and blood cultures are clear. The ID physician receives a call from the primary team that the patient is very active and does not want to be connected to an IV line all day. Which antimicrobial (at an appropriate dose) would be ideal for treating this patient based on available literature and ease of dosing?

a. Ceftriaxone

b. Cefazolin

c. Oxacillin

d. Nafcillin

Which antimicrobial (at an appropriate dose) would be ideal for treating this patient based on available literature and ease of dosing?

Ceftriaxone 0%

Cefazolin 0%

Oxacillin 0%

Nafcillin 0%

4. A patient with MSSA bacteremia secondary to a skin abscess is on your ID consult service. They are medically optimized, cultures have cleared, and they are ready for discharge. Their skin abscess was surgically drained, and the culture was growing MSSA. Of note, the patient works 2 part-time jobs and has 3 young children. They do not have a partner or any family support available and the nearest infusion center is a 45-minute drive from the patient's home, therefore they will need to self-administer their antibiotics at home. What is the most appropriate antibiotic choice (at a proper dose) for this patient?

a. Cefazolin

b. Nafcillin

c. Oxacillin

d. Ceftriaxone

What is the most appropriate antibiotic choice (at a proper dose) for this patient?

Cefazolin 0%

Nafcillin 0%

Oxacillin 0%

Ceftriaxone 0%

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- Critique

Treatment of Methicillin-Sensitive *Staphylococcus aureus*: What Does Ceftriaxone Bring to the Table?

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