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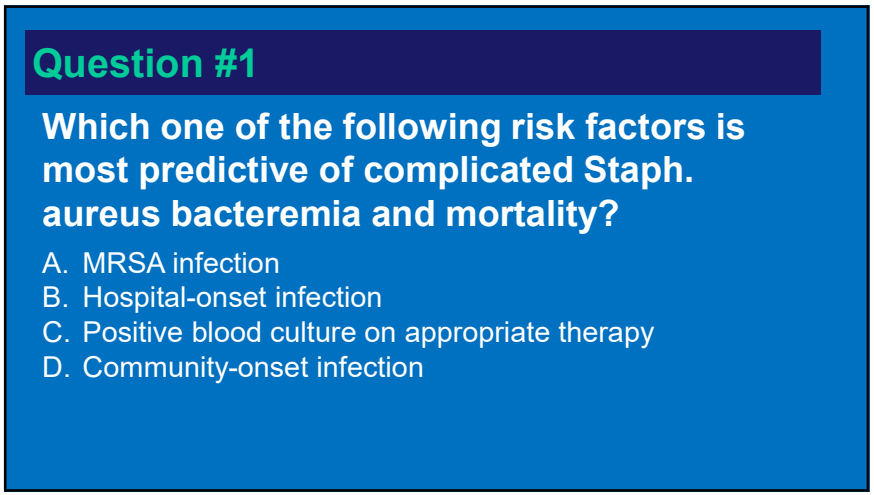

4

Question #1

Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia and mortality?

A. MRSA infection
B. Hospital-onset infection
C. Positive blood culture on appropriate therapy
D. Community-onset infection

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Predictors of Complicated/High Risk SAB*

Fowler, et al (OR)	**Liu, et al** (IDSA MRSA)	**van der Vaart, et al** (OR)
Persistent bacteremia (5.6)	Persistent bacteremia	Persistent bacteremia (6.8)
Skin findings (2.04)	Skin findings	Community onset (2.9)
Community onset (3.1)	Prosthetic material	(infected) Prosthetic material (2.3)
Persistent fever (2.2)	Persistent fever	

Complicated/High Risk = mortality, metastatic foci or complicated local infection, embolic stroke, recurrent bacteremia

OR = Odds ratio

Fowler, et al. Arch Intern Med. 2003; 163:2066;
Liu, et al. Clin Infect Dis. 2011; 52:e18-55;
van der Vaart, et al. Clin Infect Dis. 2023 Dec 29:ciad784. doi: 10.1093/cid/ciad784

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Low Risk for Complicated Bacteremia

Absence of **ALL** of the following:

- Community acquisition
- Implanted prosthetic material
- Failure to remove a central venous catheter
- Positive blood cultures beyond 48h on therapy
- Fever ≥ 38ºC for more the 72h on therapy
- Treatment delay for > 48h with signs of infection
- Clinical signs of metastatic infection

Note: Only 9.9% of bacteremias (377/3801); no IVDU, no MRSA; 84% line, skin, 9.1% unknown; median duration of therapy 15 days, 10% infection related mortality/relapse (1) @ 90 days

Hendriks. Clin Infect Dis. 2024; 79:43

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Question #2

A single positive blood culture for Staph. aureus?

A. Represents contamination in a quarter or more of cases
B. Is associated with a significantly lower relapse rate than presence multiple positive blood cultures
C. Is associated with complicated bacteremia at a rate similar to multiple positive cultures
D. Excludes the need to perform echocardiography to rule out endocarditis
E. Is associated with a lower 60-day mortality than multiple positive blood cultures

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Question #2

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C. Is associated with complicated bacteremia at a rate similar to multiple positive cultures
D. Excludes the need to perform echocardiography to rule out endocarditis
E. Is associated with a lower 60-day mortality than multiple positive blood cultures

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Single positive blood culture for S. aureus

- Represents contamination in < 10% of cases
- Follow-up blood cultures will be positive in ~15% of cases in whom half will be afebrile
- Carries similar risks of mortality, relapse, and complicated bacteremia as multiple positive cultures
- Although the risk of endocarditis is less than with multiple positive cultures (~ 4% vs ~14%), an ECHO still should be obtained
- **Always obtain follow-up blood cultures**

Infect Dis 2020;52:207, OFID. 2021;9(2):ofab642

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Echocardiography (ECHO)

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Role of Echocardiography for S. aureus Bacteremia

- Prevalence of endocarditis 12%-18% overall
- Depends on the pre-test probability
  - STROBNGLY consider TTE (sensitivity 70%, specificity 95%) in all patients with SAB
  - Obtain TEE (sensitivity 90%, specificity 95%) in high risk patients
    - Embolic events, intracardiac device, IVDU, prior IE
    - Suspected endocarditis, negative TTE

OFID Nov 24, 4:ofx261, 2017; Clin Micro Infect 23:900, 2017

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FDG-PET/CT in Patients with Staph. aureus Bacteremia

- In conjunction with TEE PET/CT increases sensitivity of Duke criteria for definite PVE
- Can identify occult foci of metastatic infection, rule out others
- May improve outcome through better source control and use of longer treatment courses
- Evidence comes entirely from observational studies and subject to bias, such as immortal; time bias

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Treatment of MSSA Bacteremia

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Question #3

On day 9 of nafcillin therapy for complicated methicillin-sensitive S. aureus bacteremia the patient has developed new neutropenia (1,000 neutrophils). MICs (µg/ml) of the blood isolate are penicillin 0.12 (S), cefazolin 0.5 (S), vancomycin 1 (S), daptomycin 0.5 (S), ceftaroline 0.5 (S).

Which one of the alternative agents would you recommend?

A. Penicillin
B. Cefazolin
C. Vancomycin
D. Daptomycin

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Which one of the alternative agents would you recommend?

A. Penicillin
B. Cefazolin
C. Vancomycin
D. Daptomycin

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FDA-approved Antibiotics for SAB

- Penicillin
- Nafcillin/Oxacillin
- Cefazolin
- Vancomycin
- Daptomycin
- Ceftobiprole

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Antibiotics for MSSA Bacteremia

Drug	Pros	Cons
Nafcillin, Oxacillin, etc	Proven efficacy, first-line agent	Q4h administration, adverse events are common
Cefazolin	Well, tolerated, q8h dosing, efficacy probably comparable to ASPs	Concern for treatment failure in high inoculum infections
Penicillin	Efficacious, better tolerated than anti-staphylococcal penicillins	Beta-lactamase negative strains only
Vancomycin	Option for patients who are not candidates for beta-lactam therapy, q12h dosing	Less efficacious than beta-lactams, nephrotoxic, requires therapeutic drug monitoring
Daptomycin	Option for patients who are not candidates for beta-lactam therapy, q24h dosing	Probably less efficacious than beta-lactams, treatment-emergence resistance

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What about Penicillin G for Penicillin-Susceptible SAB? Probably Yes

- Confirm susceptibility
  - MIC $\leq$ 0.025 µg/ml (J Antimicrob Chemother. 2021; PMID: 33615356)
  - MIC $\leq$ 0.12 µg/ml (CLSI breakpoint) and
    - Negative PCR for beta-lactamase gene (blaZ) or
    - Negative zone test
- References supporting efficacy
  - J Antimicrob Chemother. 2023; PMID: 37596905
  - Int J Antimicrob Agents. 2022; PMID: 35288257
  - Int J Antimicrob Agents. 2019; PMID: 31181352

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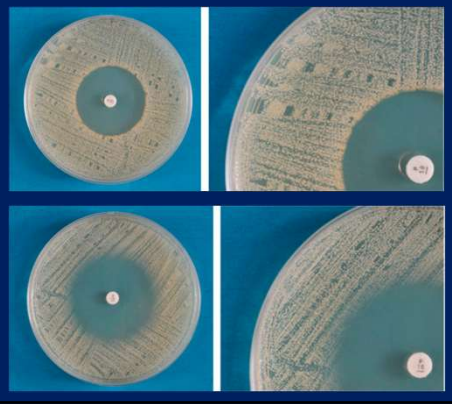
Zone Edge Test for β-lactamase

Positive

Negative



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Summary: MSSA bacteremia

- An ASP and cefazolin overall preferred agents for definite therapy
  - An ASP is first-line but less well tolerated than cefazolin
  - Observational studies suggest mortality, relapse, and treatment failures rates are similar with cefazolin
  - Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients
  - Start with an ASP until source control established
- Vancomycin, daptomycin if serious beta-lactam allergy or intolerance and possibly for OPAT (daptomycin > vancomycin)
- Ceftriaxone not 1st or 2nd line, should be avoided in patients with endocarditis, more serious infections, complicated/high risk SAB

*ASP = antistaphylococcal penicillin

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Treatment of MRSA Bacteremia

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Therapy for MRSA bacteremia

- Vancomycin
  - Dosed at 30-60 mg/kg/d
  - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
  - Need for therapeutic drug monitoring
- Daptomycin
  - FDA approved dose: 6 mg/kg q24h, recommended dose: 10 mg/kg q24h
  - Non-inferior to vancomycin, better tolerated
  - Potential for emergence of resistance on therapy (mprF mutants), especially in high inoculum infections, poor source control
  - Do not use for primary pneumonia (OK for septic emboli)
  - Some cross-resistance with VISA
- Ceftobiprole – recently FDA approved

Tong, et al: JAMA. 2025. PMID: 40193249

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Vancomycin or Daptomycin?

- Meta-analysis, 24 studies, MRSA and MSSA, heavily weighted to retrospective studies
- Microbiological cure (n=1036): favored daptomycin
- Clinical cure (n=888): favored daptomycin
- Relapse (n=878): not significantly different
- Mortality (n=8845): not significantly different
- Adverse events: favored daptomycin

Int J Antimicrob Agents. 2023, 62:106946

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Other Antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome; bacteriostatic Bone marrow suppression
Ceftaroline	SSTI, CAP	Rash, usual cephalosporin reactions, neutropenia
Dalbavancin	SSTI	Single dose or 2 doses a week apart Lipoglycopeptide, related to teicoplanin
Ceftobiprole	FDA approved SSTI, SAB	Non-inferior to daptomycin in RCT of MSSA and MRSA bacteremia (NEJM 2023;389:1390)

SSTI = skin and soft tissue infection, HAP = hospital-acquired pneumonia, VAP = ventilator-associated pneumonia
CAP = community-acquired pneumonia

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Question #4

A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

Which one of the following would you recommend?

A. Ceftaroline
B. Dalbavancin
C. Telavancin
D. Vancomycin
E. Linezolid

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Question #4

A patient with complicated MRSA bacteremia on day 9 of therapy with daptomycin q48h develops myalgias with a creatinine kinase of 1250 u/L (upper limit of normal 200). The last positive blood culture was on day 3 of therapy. MICs (µg/ml) of the isolate are as follows: vancomycin 2 (S), daptomycin 0.5 (S), dalbavancin 0.25 (S), telavancin 0.5 (S), ceftaroline 1 (S).

Which one of the following would you recommend?

A. Ceftaroline
B. Dalbavancin
C. Telavancin
D. Vancomycin
E. Linezolid

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But What About That Vancomycin MIC Of 2 Mg/Ml?

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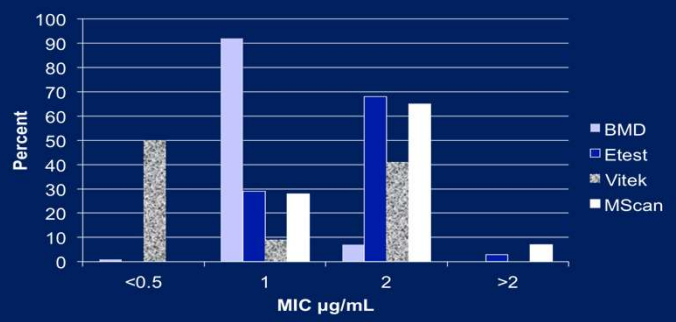
Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

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Highlights of Modern Vancomycin Dosing for MRSA Infections

- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 mg∗h/L(assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24
- Consider loading dose for more seriously ill patients
  - Intermittent infusion: 30-35 mg/kg, max 3000 mg (actual body weight), then 15-20 mg/kg q8-12h
  - Continuous infusion: 15-20 mg/kg then 30-60 mg/kg, target steady state of 20-25 μg/ml
- Pediatric doses higher: 60-80 mg/kg/d divided q6-8h

Am J Health-Syst Pharm. 2020;77:835-864

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Duration of Therapy for S. aureus BSI

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Duration of Therapy for S. aureus BSI

14 days

- UNCOMPLICATED/LOW RISK (~20% of cases)
- Fever resolves by day 3
- **Sterile blood culture after 1-2 days (DOCUMENT!)**
- **Easily removed focus of infection (no DVT)**
- **No metastatic infection (e.g., osteo)**
- **Neg. echo, no evidence of endocarditis, no abnormal valve**
- No implanted prosthetic devices, no DM, no immunosuppression

4-6 weeks +

- COMPLICATED/HIGH RISK
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

Adapted from Fowler, Ann Intern Med 163:2066, 2003

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Oral Therapy of S. aureus BSI

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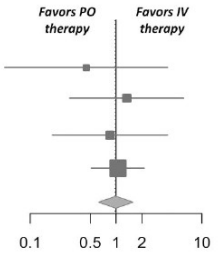
Meta-Analysis: Oral Therapy of S. aureus Bacteremia

Study	PO therapy	IV therapy	RR (95% CI)
	Treatment Failure		
Heldman et al 1996	1/19 (5%)	3/25 (12%)	0.44 (.05–3.89)
Schrenzel et al 2004	5/30 (17%)	2/16 (13%)	1.33 (.29–6.12)
Iverson et al 2019	3/47 (6%)	3/40 (8%)	0.85 (.18–3.98)
Kaasch et al 2024	14/108 (13%)	13/105 (12%)	1.05 (.52–2.12)
Random effects model			**0.99 (.63–1.57)**

Heterogeneity: $I^2 = 0\%$, $\tau^2 = 0$, $P = .86$



Clin Infect Dis. 2025; 80:29.

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SABATO RCT: Oral Step-down vs IV for "Low Risk" SAB

- 5063 patients screened, 4696 did not meet eligibility criteria, 206 enrolled
- 5-7 days IV
  - Flucloxacillin, cloxacillin, cefazolin, vancomycin for MSSA
  - Vancomycin or daptomycin for MRSA
- Randomized at day 5-7 to complete 14 days of therapy
  - IV regimen as above **OR**
  - Oral regimens: TMP/SMX 160/80 mg q12h (MSSA, MRSA) or Clindamycin 600 mg q8h (MSSA) or Linezolid 600 mg q12h (MRSA)
- 8% MRSA
- 90% central (23%) or peripheral catheter (44%), skin, soft tissue infection (23%)
- Study terminated at 50% planned enrollment, 10% (vs original 2.5%) non-inferiority margin

TMP/SMX = trimethoprim/sulfamethoxazole

Lancet ID. 2024; 2024 Jan 17:S1473-3099(23)00756-9

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SABATO Trial: Oral (PO) Step-down vs IV Therapy for "Low Risk" SAB

Outcomes	PO (n=108)	IV (n=105)
SAB complication @ 90 days	14 (13%)	13 (12%)
Relapse	3 (3%)	4(4%)
Deep-seated infection	5 (5%)	8 (8%)
Death due to SAB	2(2%)	0
Missing/non-attributable death	8 (7%)/3 (3%)	5(5%)/1 (1%)

Lancet ID. 2024; 2024 Jan 17:S1473-3099(23)00756-9

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Question #5

A Case of MSSA Bacteremia

37-year-old M, diabetic, moderate chronic kidney disease, admitted to the intensive care unit for diabetic ketoacidosis. Internal jugular central line placed.

D3: awaiting transfer to the floor he spikes a fever to 38.9oC, P 105, vital signs otherwise normal. Non-focal exam. Chest x-ray negative, urine 2+ protein. Blood culture (BC) x2 sent, vancomycin and cefepime begun.

D4: Both D3 BC+ GPCs (Gram-positive cocci) in clusters. BCx2 sent. Afebrile.

D5: D3 BC+ MSSA, penicillin resistant. D4 2/2 BC+ GPCs in clusters. BCx2 sent, central line removed, and antibiotics changed to cefazolin.

D6: D4 BC+ MSSA, 1 of 2 D5 BC+ for GPCs in clusters. BCx2

D7: 1 of 2 D5 BC+ MSSA, D6 BC no growth. BCx2 sent.

D8-10: TTE negative. D6 BC and all subsequent BC no growth.

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Question #5

Which one of the regimens would you recommend for definitive therapy of the MSSA bacteremia?

A. 7 days of cefazolin IV then clindamycin 600 mg PO TID for 7 days
B. 14 days of cefazolin IV
C. 14 days of cefazolin IV then clindamycin 600 mg PO TID for 7 days
D. 14 days of cefazolin IV then clindamycin 600 mg PO TID for 14 days
E. 28 days of cefazolin IV

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Which one of the regimens would you recommend for definitive therapy of the MSSA bacteremia?

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D. 14 days of cefazolin IV then clindamycin 600 mg PO TID for 14 days
E. 28 days of cefazolin IV

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Oral Therapy of S. aureus Bacteremia

- Only a single randomized clinical trial (RCT), somewhat low in quality
- Observation studies subject to selection bias, confounding by indication
  - Mortality and relapse rates consistently higher with IV!! Really!?
- Role in treatment of and efficacy for endocarditis, endovascular infections, complicated bacteremia, MRSA in particular is emerging
- May be an option for treatment of “low risk” patients, but there is a lack of standard definition
- **Infectious disease consultation strongly recommended for all SAB!**
- Prefer agents with good oral bioavailability: linezolid, TMP/SMX, fluoroquinolone + rifampin, clindamycin, anti-staphylococcal beta-lactam (?)

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Combination Therapy of S. aureus BSI

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Question #6

Which one of the following combinations have been shown to improve mortality of patients with S. aureus bacteremia or native valve endocarditis?

A. Anti-staphylococcal beta-lactam + gentamicin for MSSA
B. Anti-staphylococcal beta-lactam + rifampin for MSSA
C. Vancomycin + a beta-lactam for MRSA or MSSA, pending cultures
D. Daptomycin + fosfomycin for MRSA
E. No combination regimen

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Which one of the following combinations have been shown to improve mortality of patients with S. aureus bacteremia or native valve endocarditis?

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D. Daptomycin + fosfomycin for MRSA
E. No combination regimen

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Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	PMID
Adjunctive rifampin	RCT	MRSA,MSSA	No benefit	1929035 29249276
Adjunctive aminoglycoside	Obs, RCT	MRSA,MSSA	1d shorter SAB, toxic	Various
Adjunctive dapto	RCT	MSSA	No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	↑↑ AKI, higher mortality	32044943
Dapto + ceftaroline	Obs, aborted RCT	MRSA	Low quality data	30858203 31640977 31404468
Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985
β-lactam + ertapenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration ↓ by 25h	38946294

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

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Adjunctive rifampin	RCT	MRSA,MSSA	No benefit	
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Adjunctive dapto	RCT	MSSA		32667982
Adjunctive β-lactam + vanco/dapto	RCT	MRSA	…, higher mortality	32044943
Dapto + ceftaroline	Ob…		Low quality data	30858203 31640977 31404468
Dapto + f…	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985
…ertapenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration ↓ by 25h	38946294

Consider for salvage therapy, not first line

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events

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De-escalation of Combo Therapy for Complicated MRSA bacteremia

Outcome	Combo (n=66)	Mono (n=74)
Composite clinical failure	14 (21%)	8 (24%)
Relapse bacteremia, 60d	2 (3%)	5 (7%)
In-patient mortality	1 (2%)	4 (5%)
Readmission, 60d	13 (20%)	13 (18%)
Duration of bacteremia, d	8 (IQR 6-11)	8 (IQR 5-12)
Adverse drug event	2 (4%)	1 (1)
Length of stay, d	26 (IQR 20-41)	24 (IQR 16-33)

Open Forum Infect Dis. 2021 Jun 22;8(7):ofab327.

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Take-Home Points

- "Uncomplicated" Bacteremia is uncommon
  - TTE for all
  - 2 weeks of therapy for "low risk" SAB, otherwise 4-6 weeks
- Parenteral drugs of choice
  - MSSA: Nafcillin, cefazolin, penicillin
  - MRSA: Daptomycin, vancomycin
- Role of oral therapy is an evolving area
- Monotherapy is effective in most cases, reserve combination therapy for salvage

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Thanks

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