



Staphylococcal Diseases: Bacteremia

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Merck - Stock and DSMB member
- Moderna - Stock

Outline of the Talk

- Risk factors for poor outcome, complicated bacteremia
- Imaging
- Treatment of MSSA bacteremia
- Treatment of MRSA bacteremia
- Combination therapy
- Oral Therapy
- Duration of Therapy

MSSA = Methicillin-susceptible *S. aureus*, MRSA = Methicillin-resistant *S. aureus*

What Complicated SAB Is

- Infection-related mortality
- Metastatic or locally complicated infections
- Embolic stroke
- Recurrent bacteremia

Arch Intern Med 163:2066, 2003

Risk Factors for Poor Outcome, Complicated *S. aureus* Bacteremia (SAB)

Case Study

- A 36-year-old female with opioid use disorder on methadone maintenance is admitted for altered mental status
- She is afebrile and vital signs are normal
- On exam she is arousable but somnolent and there is an erythematous, fluctuant lesion of the R groin, no heart murmur is heard
- Gram stain of the pus shows gram-positive cocci in clusters
- Vancomycin is administered
- The next day she is more alert and reports a week of fevers for which she took some unknown antibiotic given to her by a friend
- 1 of 2 blood cultures from admission is growing Gram-positive cocci in clusters

Question #1

Which of the following is true of a single positive blood culture for *S. aureus*?

- A. Represents contamination in a quarter or more of cases
- B. Is associated with complicated bacteremia at rates similar to that for multiple positive blood cultures
- C. Is most likely to represent uncomplicated bacteremia
- 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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- C. **Is most likely to represent uncomplicated bacteremia***
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- E. Is associated with a lower 60-day mortality than multiple positive blood cultures

Question #2

Which of the following risk factors is most associated with complicated *S. aureus* bacteremia?

- A. MRSA infection
- B. Community-acquired infection
- C. Persistence of bacteremia beyond 48 hours
- D. Injection drug use
- E. Presence of a prosthetic joint replacement

Question #2

Which of the following risk factors is most associated with complicated *S. aureus* bacteremia?

- A. MRSA infection
- B. Community-acquired infection
- C. Persistence of bacteremia beyond 48 hours***
- D. Injection drug use
- E. Presence of a prosthetic joint replacement

Risk Factors for Complicated Bacteremia

- Persistently positive blood cultures on therapy (48-72h) (endovascular source, metastatic focus)
- Community-onset of bacteremia (10-15% endocarditis rate)
- Presence of an intracardiac device (prosthetic valve, CIED) (endocarditis)
- Injection drug use (endocarditis)
- Note: 60-70% of all *S. aureus* bacteremia is complicated

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. 2024; 78:846

Low Risk for Complicated Bacteremia

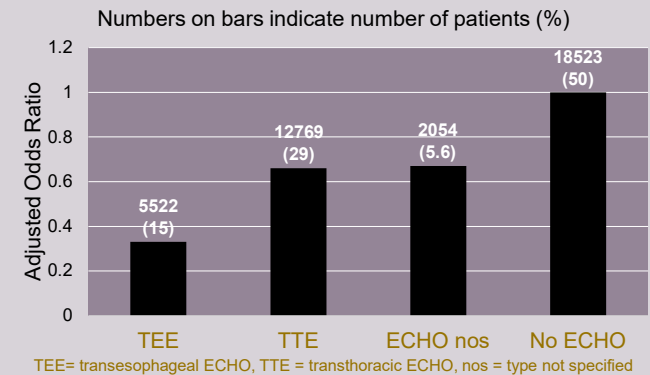
- Absence of **ALL** of the following
 - Community acquisition
 - Implanted prosthetic material
 - Failure to remove a central venous catheter
 - Positive blood cultures beyond 48h on therapy
 - Fever $\geq 38^{\circ}\text{C}$ for more the 72h on therapy
 - Treatment delay for > 48h with signs of infection

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

Hendriks, Clin Infect Dis. 2024; 79:43

Imaging

ECHO and Mortality in SAB



SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

VAH Study, JAMA Intern Med 177:1489, 2017

Prediction Scores to Rule-out Endocarditis (and avoid an ECHO) in Patients with S. aureus Bacteremia (SAB)

POSITIVE (Cutoff >4)	PREDICT (Cutoff ≥2)	VIRSTA (Cutoff ≥3)
TTP < 9h – 13h (2,3,5)	ICD (2)	Emboli (5)
IVDU (3)	Pacemaker (3)	Meningitis (5)
Vascular phenomena (6)	CA SAB (2)	Intracardiac device (4)
Predisposing heart dis (5)	HCA SAB (1)	Previous IE (3)
	Positive BC > 72h (2)	IVDU (4)
		Positive BC > 48h (3)
		CA or HCA SAB (2)
		Sepsis or septic shock (1)
		CRP > 190 mg/L (1)

TTP = time to positivity of blood culture, IVDU = IV drug use, ICD = intracardiac device, CRP = C-reactive protein

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Clin Infect Dis 2022; 74:1442, J Antimicrob Chemother 2022; 77: 2003, J. Clin. Med. 2022; 11: 1502.

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Prevalence of endocarditis 12%-18% overall
Prevalence of endocarditis with a negative score 2.2-4.9%

Role of Echocardiography for SAB

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

OFID 2017; 4:ofx261; Clin Micro Infect 2017; 23:900

¹⁸FDG-PET/CT in Patients with *S. aureus* Bacteremia

- Caveats
 - No randomized trials, only observational studies, hence subject to bias
 - Criteria for who gets the study ill-defined, vary widely
- Detects additional sites of infection not clinically suspected in ~50%-70% of patients, rules out some sites (~50%)
 - Many of new foci are found in patients with a known prior focus
 - 10% undergo an intervention other than more imaging
 - 30% have a change in antimicrobial duration or dosing
- No mortality benefit if immortal time bias is accounted for
- No reduction in relapse rates

PET/CT = ¹⁸F-fluorodeoxyglucose Positron Emission Tomography/Computed Tomography

Clin Infect Dis. 2021; 73:e3859, Eur J Clin Microbiol Infect Dis. 2025; 44:895

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 (see "Imaging")
- **Always obtain follow-up blood cultures**

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

Treatment of Bacteremia Caused by MSSA

Back to Case Study #1

- A 36-year-old female with opioid use disorder on methadone maintenance is admitted for altered mental status
- She is afebrile and vital signs are normal
- On exam she is arousable but somnolent and there is an erythematous, fluctuant lesion of the R groin, no heart murmur is heard
- Gram stain of the pus shows gram-positive cocci in clusters
- Vancomycin is administered
- The next day she is more alert and reports a week of fevers for which she took some unknown antibiotic given to her by a friend
- 1 of 2 blood cultures from admission is growing Gram-positive cocci in clusters

1 of 2 blood cultures from admission is positive for MSSA with the following MICs: oxacillin 0.5 mg/ml, penicillin 0.125 mg/ml, vancomycin 0.5 mg/ml, daptomycin 0.5 mg/ml, dalbavancin 0.06 mg/ml. Repeat blood cultures show no growth to date.

Question #3

Which antibiotic would you recommend for this patient?

- A. Nafcillin
- B. Cefazolin
- C. Penicillin
- D. Vancomycin
- E. Dalbavancin

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- C. Penicillin
- D. Vancomycin
- E. Dalbavancin

(Seriously Outdated) AHA Guidelines: MSSA Native Valve Endocarditis

- Preferred regimens
 - Nafcillin (or Oxacillin) 2 gm q4h x 6 weeks
 - Cefazolin 2 gm q8h x 6 weeks, allergic or intolerant to naf
 - No aminoglycoside
 - Avoid penicillin
- Serious/immediate hypersensitivity reaction, intolerance to above
 - Document allergy, desensitize OR
 - Vancomycin 30-60 mg/kg/d divided q8-12h
 - Daptomycin 6-10 mg/kg q24h x 6 weeks

Circulation 2015; 132:1435

Beta-lactam vs. Vancomycin for MSSA Bacteremia (122 VA Hospital Study) - Multivariable Analysis

Variable	Mortality, Hazard Ratio (95% CI)
Beta-lactam* vs. Vancomycin	0.65 (0.52-0.80)
ASP or cefazolin vs. Vancomycin	0.57 (0.46-0.71)

*44% ASP (nafcillin or oxacillin), 30% cefazolin

ASP = anti-staphylococcal penicillin, 30% cefazolin

Clin Infect Dis 2015; 61:361

MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

- Efficacy:
 - Penicillinase inoculum effect on cefazolin MICs
 - A potential concern in high-inoculum infections (endovascular infections, multiple/large abscesses)
- Safety:
 - Adverse events due to ASPs > cefazolin

Cloxacillin vs. Cefazolin for MSSA Bacteremia

- Open-label multicenter non-inferiority (12%) RCT of MSSA bacteremia
 - Exclusions: CNS or implant infections, >72h prior treatment
 - Cloxacillin (12 g/d) or Cefazolin (6 g/d) for ≥ 7 days, then standard of care
 - Composite primary endpoint: sterile blood cultures at day 3 (day 5 for endocarditis), no relapse, alive, and clinical success at day 90 in ITT population
- Types of infection
 - Bacteremia, unknown focus: 30%
 - Catheter-related: 37%
 - SSTI: 22%
 - Bone or joint: 25%
 - Endocarditis: 5%

RCT = Randomized Controlled Trial

Lancet. 2025 Nov 15;406:2349

Outcomes

Outcome Measure	Cefazolin (n=146)	Cloxacillin (n=146)	Δ (95%CI)
Primary	109 (75%)	108 (74%)	1% (-11 to 9)
Survival, 90 d	134 (92%)	134 (92%)	0% (-7 to 7)
Micro success, d3/5	136 (93%)	135 (92%)	1% (-6 to 7)
No relapse, 90 d	145 (99%)	144 (99%)	1% (-3 to 4)
Clinical success, 90 d	116/144 (81%)	111/139 (80%)	1% (-9 to 10)
Clinical success, 7 d	105/142 (74%)	98/140 (70%)	4% (-6 to 14)
Any SAE	51 (36%)	64 (44%)	-9% (-20 to 2)
SAE by day 7	14 (10%)	30 (20%)	-11 (-19 to -3)
AKI, day 7	1/134 (1%)	15/128 (12%)	-11% (-18 to -6)
AKI, end of study Rx	4/111 (4%)	17/99 (17%)	-13% (-23 to -6)

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Cefazolin Inoculum Effect (CzIE)

- Beta-lactamase-mediated increase in broth dilution MIC to ≥ 16 $\mu\text{g/ml}$ at high inoculum (5×10^7 cfu/ml instead of 5×10^5 cfu/ml)
 - Type C and type A beta-lactamases most common, ~ 30-40% for each
 - ~30-50% of type C allotype exhibits CzIE
 - ~80+ % of type A allotype exhibits CzIE
 - Associated with reduced efficacy in animal models and treatment failure in patients treated with cefazolin
- cfu = Colony-forming Units

Antimicrob Agents Chemother. 2020; 64:e02511-19. PMID: 32071048; Open Forum Infect Dis. 2018; 5:ofy123. PMID: 29977970; Antimicrob Agents Chemother. 2013; 57:4276. PMID: 23796934; J Infect Dis. 1983; 147:1078. PMID: 6602190.

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

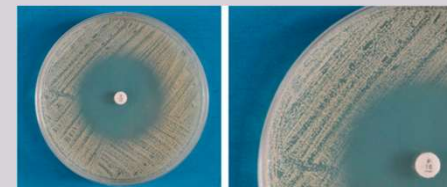
- Confirm susceptibility
 - MIC ≤ 0.025 $\mu\text{g/ml}$ (J Antimicrob Chemother. 2021; PMID: 33615356)
 - MIC ≤ 0.125 $\mu\text{g/ml}$ (CLSI breakpoint) and
 - Negative PCR for beta-lactamase gene (blaZ) or
 - Negative zone test
- References supporting efficacy
 - J Antimicrob Chemother. 2023; PMID: 37596905
 - Int J Antimicrob Agents. 2022; PMID: 35288257
 - Int J Antimicrob Agents. 2019; PMID: 31181352

Zone Edge Test for β -lactamase

Positive



Negative



What about Dalbavancin?

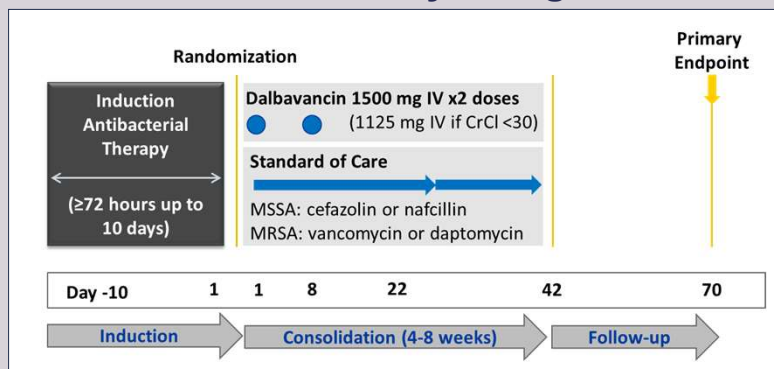
Research

JAMA | Original Investigation

Dalbavancin for Treatment of *Staphylococcus aureus* Bacteremia The DOTS Randomized Clinical Trial

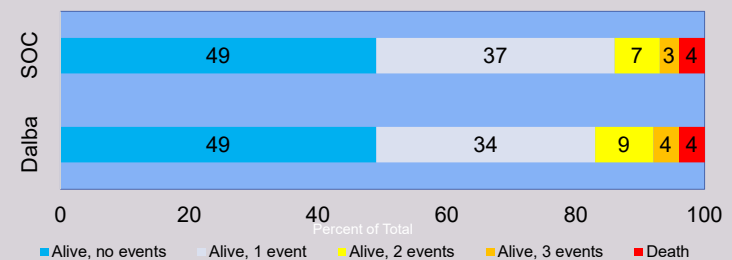
JAMA. 2025; 334:866-877. PMID: 40802264

Methods: DOTS Study Design



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Desirability of Outcome Ranking (DOOR) at Day 70



Events: Clinical failure, infectious complication, SAE or AE with study discontinuation

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Secondary Outcome: Clinical Efficacy, 70 day

Outcomes	Dalbavancin (n=100)	SOC (n=100)
Clinical success	73	72
Relapse	2	6
Infectious complication	7	4
Inadequate response	3	0
Dead	4	4
Missing	11	14

SOC = Standard of Care

Summary: MSSA bacteremia

- One RCT confirms those of prior observational studies
 - Antistaphylococcal penicillins (ASP) and cefazolin have comparable efficacy
 - ASP more toxic than cefazolin
 - Consider starting with an ASP in those with high inoculum infections until source control established
- Penicillin is an option after excluding presence of beta-lactamase
- Dalbavancin as a 2-dose, outpatient regimen in stable patients
- Vancomycin, daptomycin if serious beta-lactam allergy or intolerance and possibly for OPAT (daptomycin > vancomycin)
- Ceftriaxone not 1st or 2nd or 3rd line, avoid

Treatment of Bacteremia Caused by MRSA (Methicillin-Resistant *S. aureus*)

Case Study #2

- A 67-year-old male with poorly controlled type 2 diabetes is admitted for fever, chills, and myalgias
- A 3/6 systolic murmur is present at the cardiac apex
- He was empirically treated with vancomycin + ceftriaxone
- 1 of 2 blood cultures obtained on hospital day 2 is positive for GPCs in clusters
- 3 of 3 blood cultures from admission are positive for MRSA with the following antibiotic susceptibilities

Vancomycin 2 mg/ml, daptomycin 0.5 mg/ml, dalbavancin 0.06 mg/ml, ceftaroline 1 mg/ml, ceftobiprole 2 mg/ml

Question #4

What antibiotic regimen would you recommend for this patient?

- A. Vancomycin
- B. Vancomycin + rifampin
- C. Daptomycin
- D. Daptomycin + ceftaroline
- E. Ceftaroline

Question #4

What antibiotic regimen would you recommend for this patient?

- A. Vancomycin
- B. Vancomycin + rifampin
- C. Daptomycin
- D. Daptomycin + ceftaroline***
- E. Ceftaroline

First-line Choices for MRSA Bacteremia

- Vancomycin
 - 30-60 mg/kg/d in 2-3 divided doses
 - Nephrotoxic at higher trough concentrations (15-20 µg/ml)
 - Need for therapeutic drug monitoring
 - Daptomycin
 - Non-inferior in registrational RCT, better tolerated than vancomycin,
 - Potential for emergence of resistance on therapy (mprF mutants), especially in high inoculum infections, poor source control
 - Do not use for primary pneumonia
 - Some cross-resistance with VISA
- VISA = Vancomycin-Intermediate *S. aureus*

JAMA: 2014; 312:1330

Vancomycin or Daptomycin?

- Meta-analysis, 24 studies, MRSA and MSSA, heavily weighted to retrospective studies
- Microbiological cure (n=888): favored daptomycin
- Clinical cure (n=1036): favored daptomycin
- Relapse (n=838): not significantly different
- Mortality (n=8845): not significantly different
- Adverse events: favored daptomycin

Int J Antimicrob Agents. 2023; 62:106946

Vancomycin Dosing for MRSA Infections

- Use of troughs out of favor
- Target AUC/MIC_{MED} to 400-600 mg•h/L (assume MIC_{BMD} = 1 µg/ml)
 - Bayesian-derived monitoring, 1-2 samples (C_{max}, C_{min})
 - 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

BMD = broth microdilution

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

What if the Vancomycin MIC = 2 µg/ml?

- Poor predictor of outcome (JAMA 2014; 312:1552)
- MIC result is method dependent (Int J Antimicrob Agents. 2008; 32:378)
 - 90% of MRSA isolates have a BMD MIC of 1
 - Automatic systems and E-test skew toward MICs of 2
- No reason to change therapy on its own

BMD = broth microdilution

Combination Therapy of SAB

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
Cefazolin + ertapenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration ↓ by 25h	38946294

Dapto = daptomycin, vanco = vancomycin, AKI = acute kidney injury, AE = adverse events
SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

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Adjunctive β -lactam + vanco/dapto	RCT	MRSA	Higher mortality	32044943
Dapto + ceftaroline	Obs	MRSA	Low quality data	30858203 31640977 31404468
Dapto + f	RCT	MRSA	No mortality benefit, $\downarrow$ micro failure, $\uparrow$ AEs	32725216 32887985
Dapto + meropenem	Obs	MSSA, SAB > 48h	No mortality benefit, SAB duration $\downarrow$ by 25h	38946294

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

Consider for salvage therapy, not first line

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)

* Randomized controlled trial data exist for SAB

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

CAP = community-acquired pneumonia

SEE ENLARGED SLIDE FOLLOWING ENTIRE PRESENTATION

Back to Case Study #2

- A 67-year-old male with poorly controlled type 2 diabetes is admitted for fever, chills, and myalgias. A 2/6 systolic murmur is present at the cardiac apex. He was empirically treated with vancomycin + ceftriaxone.
- Last positive blood culture was on hospital day 2. TTE and TEE negative, MRI of the spine negative. On hospital day 16 he pulls out his IV, announces he needs to be discharged from the hospital to attend to personal matters, and requests an oral regimen to complete therapy for the MRSA bacteremia
- MRSA susceptibilities: linezolid 2 mg/ml, TMP/SMX < 2/38 mg/ml, rifampin 0.5 mg/ml, levofloxacin < 0.5 mg/ml, clindamycin < 0.5 mg/ml

Question #5

Which oral regimen would you recommend for this patient?

- No additional therapy is needed
- Linezolid for 2 weeks more
- TMP/SMX for 2 weeks more
- Clindamycin for 2 weeks more
- Levofloxacin + rifampin for 2 weeks more

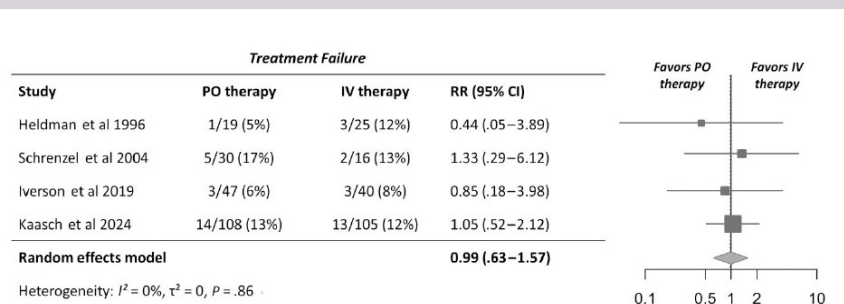
Question #5

Which oral regimen would you recommend for this patient?

- A. No additional therapy is needed
- B. Linezolid for 2 weeks more
- C. TMP/SMX for 2 weeks more***
- D. Clindamycin for 2 weeks more
- E. Levofloxacin + rifampin for 2 weeks more

Oral Step-down Therapy for *S. aureus* Bacteremia

Meta-Analysis: Oral Therapy of *S. aureus* Bacteremia



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
- Role in treatment of and efficacy for endocarditis, endovascular infections, complicated bacteremia, MRSA in particular is evolving
- Possible option for treatment of “low risk” patients, but there is a lack of standard definition of what this is
- Infectious disease consultation strongly recommended for all SAB!**
- Prefer agents with good oral bioavailability: linezolid, TMP/SMX, fluoroquinolone + rifampin, minocycline, clindamycin, anti-staphylococcal beta-lactam (?)

Duration of Therapy for SAB

14 days

UNCOMPLICATED/LOW RISK (~20% of cases)

- **Sterile blood culture after 2-3 days (DOCUMENT!)**
- Fever resolves by day 3
- **Easily removed focus of infection (no DVT)**
- **No metastatic infection**
- **No evidence of endocarditis (negative echo)**
- No predisposing valvular abnormalities
- (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

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Take-Home Points

- “Uncomplicated” bacteremia is uncommon
 - 2 weeks of therapy for “uncomplicated” SAB, otherwise 4-6 weeks
- Positive blood cultures $\geq$ 48h on therapy a risk factor for complicated
- Parenteral drugs of choice
 - MSSA: Nafcillin, cefazolin
 - MRSA: Daptomycin or vancomycin
- Dalbavancin as 2-dose “consolidation” therapy in stable patients with MSSA or MRSA who have cleared their bacteremia
- Monotherapy is effective in most cases, reserve combination therapy for salvage
- Role of oral therapy is an evolving area

Thanks