26 – Staphylococcal Disease

Speaker: Henry Chambers, MD

Staphylococcal Diseases

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Disclosures of Financial Relationships with Relevant Commercial Interests

- Equity: Moderna
- Data Monitoring Committee: Merck
- Consultant: Janssen

Outline of the Talk

- Risk factors for poor outcome, complicated bacteremia
- Echocardiography
- Treatment of MSSA bacteremia
- Treatment of MRSA bacteremia
- Combination therapy

Q1. 45 year old man, one week of back pain. He is afebrile and vital signs are normal; normal exam except for tenderness to palpation of the lower back. MRI shows L3-L4 discitis, hyperemic marrow; 1 of 3 blood cultures is positive for coagulase-negative staphylococci.
Which one of the following would you recommend?

A. Bone biopsy with culture as the blood isolate is likely a contaminant
B. Request speciation of the blood isolate
C. PET-CT to look for another focus of infection for biopsy
D. Fungal serologies, PPD

Staphylococcus lugdunensis

- Coagulase negative….
  - The tube "free" coagulase test is negative
  - The latex "bound" coagulase (i.e., clumping factor) test may be positive and confuse physicians
- Virulent, aggressive, similar to *S. aureus*.
  - Bacteremia, NV and PV endocarditis
  - Bone and joint infection
  - Pacemaker, other device-related infections
- Susceptible to many antibiotics (rarely *mecA* positive)

Risk factors for poor outcome, complicated S. aureus bacteremia

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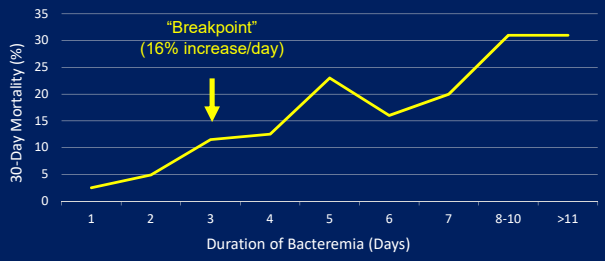
Q2. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia?

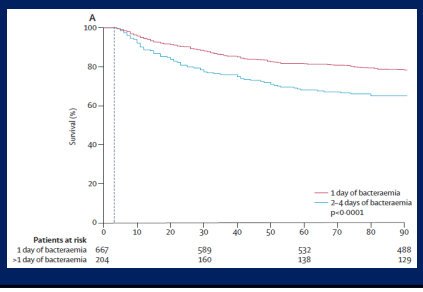
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

Longer durations of Staph. aureus bacteremia (SAB) are associated with higher the mortality



Clin Infect Dis. 2019 Apr 5. pii: ciz257. doi: 10.1093/cid/ciz257. [Epub ahead of print]

Even 2 days of Bacteremia on Therapy is Bad



Lancet Infect Dis 2020; 20: 1409

Risk factors for longer durations of Staph. aureus Bacteremia

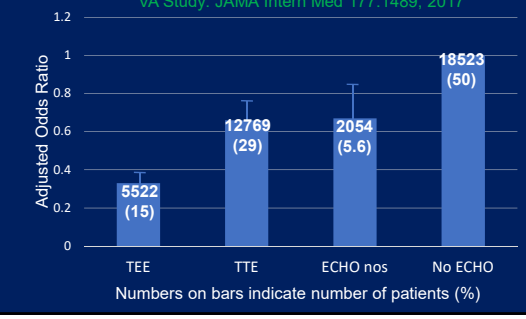
- Factors predictive of longer duration of bacteremia
  - MRSA
  - Delayed source control
- Factors **NOT** associated with longer durations of bacteremia
  - MIC
  - Choice of antimicrobial (specific agent, single or combo)
  - Switching from vancomycin to daptomycin

Clin Infect Dis. 2019 Apr 5. pii: ciz257. doi: 10.1093/cid/ciz257. [Epub ahead of print]

Echocardiography

ECHO and mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Role of echocardiography and what modality used for S. aureus bacteremia

Depends on the pre-test probability

- Consider TTE (sensitivity 70%, specificity 95%) in all patients with SAB
  - Possible exception: HCA + no intracardiac devices + no signs IE + negative BC @ 48-72h
- Obtain TEE (sensitivity 90%, specificity 95%) in high risk patients
  - Embolic events, intracardiac device, IVDU, prior IE
  - Suspected endocarditis, negative TTE

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

Treatment of MSSA Bacteremia

Q3. 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

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)

Clin Infect Dis 61:361, 2015

Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

…the current laboratory screening procedures for detecting penicillin susceptibility may not be reliable.

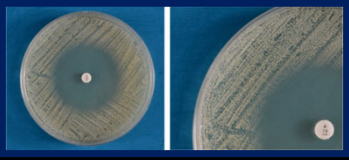
Pen MIC (µg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

Negative



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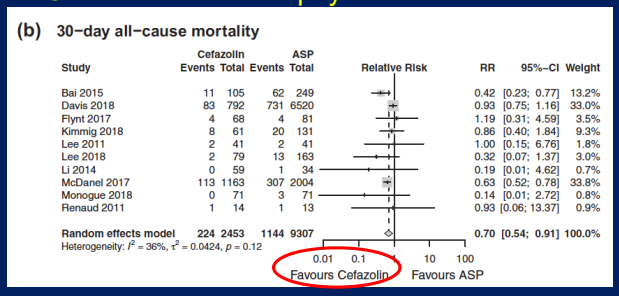
MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

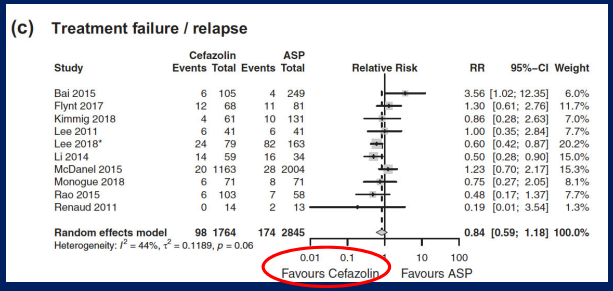
- Efficacy:
  - Penicillinase inoculum effect on cefazolin MICs – does it matter?
- Safety :
  - Adverse events due to ASPs

Cefazolin vs Anti-staphylococcal Penicillins



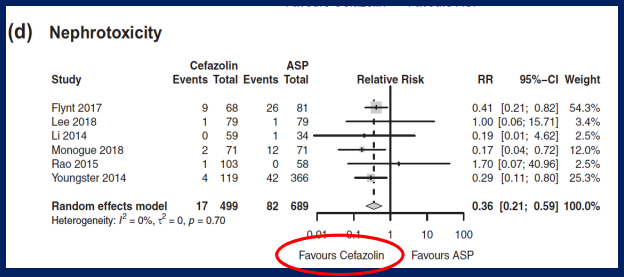
Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins



Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins



Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin Inoculum Effect (CzIE*) in 3 Hospitals in Argentina

*Beta-lactamase-mediated increase in broth dilution MIC to ≥ 16 µg/ml at high inoculum (5 x 10^7 cfu/ml instead of 5 x 10^5 cfu/ml)

- Anti-staphylococcal penicillins are not available in Argentina
- Cefazolin is the primary beta-lactam used to treat MSSA
- 54.5% prevalence (42/77 patients with SAB)
  - 7-day mortality CIE pos vs CIE neg: 12% vs 6% (p=0.44)
  - 30-day mortality CIE pos vs CIE neg: 40% vs 15% (p=0.03)

Open Forum Infect Dis.018 May 23;5(6):ofy123

What about ceftriaxone for MSSA bacteremia?

- Single center, retrospective cohort
  - 38 cefazolin
    - Presumed/proven endovascular: 17 (45%), SSTI: 3 (8%)
  - 33 ceftriaxone
    - Presumed/proven endovascular: 7 (21%), SSTI: 11 (33%)
  - Outcomes
    - Treatment failure*: 11 (29%) cefazolin vs. 18 (55%) ceftriaxone; *P* = .029
    - Mortality: 1 (3%) ceftriaxone vs 4 (11%) cefazolin

* Failure = prolonged IV, unplanned oral therapy, incomplete treatment, relapse, readmission, unplanned surgery

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

What about ceftriaxone for MSSA bacteremia?

- Single center, retrospective cohort
  - 95 cefazolin/oxacillin
    - ICU admission 48%, Endocarditis 43%, SSTI 10%
  - 148 ceftriaxone
    - ICU admission 29%, Endocarditis 28%, SSTI 16%
  - Failure*: 18 (19%) cefazolin/oxacillin vs 31 (21%) ceftriaxone
  - Failure, endocarditis: 4 (10%) cefazolin/oxacillin vs 11 (26%) ceftriaxone, p = 0.11)

* Failure = 90 day mortality, readmission, micro failure

Open Forum Infect Dis. 2020 Aug 13;7(9):ofaa341
See also: Meta-analysis, Antibiotics 2020, 9, 39; doi:10.3390/antibiotics9020039

Summary: MSSA bacteremia

- Cefazolin is better tolerated than ASPs
- AHA recommends as second-line agent for native valve endocarditis
- Overall mortality no worse, may be better with cefazolin compared to ASPs
- Clinical failure rates and recurrences similar
- Anxiety over the inoculum effect, which may adversely impact outcome in a subset of cefazolin-treated patients
- Ceftriaxone efficacy poorly defined, avoid for endocarditis

Treatment of MRSA Bacteremia

Q4. 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

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)
- Daptomycin
  - Non-inferior to vancomycin
  - Treatment failures due to emergence of resistance on therapy (mprF mutants)
  - Do not use for primary pneumonia
  - Some cross-resistance with VISA

Holland et al: JAMA 312:1330, 2014

FDA-approved antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr $\leq$ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic
Ceftaroline	SSTI, CAP	Rash, usual cephalopsorin reactions

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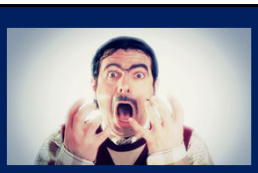
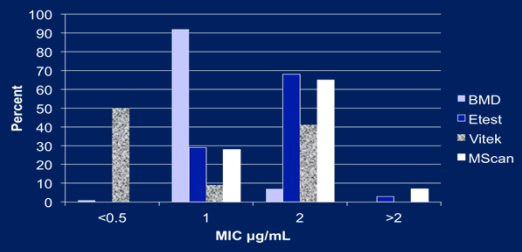
FDA-approved antibiotics for MRSA Infections

Antibiotic	Indications	Comments
Tedizolid	SSTI	May be less toxic than linezolid
Dalbavancin	SSTI	Single dose or 2 doses a week apart Lipoglycopeptide, related to teicoplanin
Oritavancin	SSTI	One time dose Lipoglycopeptide, related to vancomycin May artificially prolong PT, PTT



But what about that vancomycin MIC of 2 µg/ml?

Vancomycin MICs Vary by Method



Int J Antimicro Agent 32:378, 2008

MIC is a Poor Predictor of Outcome

- Meta-analysis, 38 studies, 8291 episodes
- MIC < 1.5 µg/mL (low) versus MIC ≥ 1.5 µg/mL (high)
- Mortality low = 25.8%, high = 26.8%
- Adjusted risk difference = 1.6% (-2.3 to 5.6%), p = 0.43

Kalil, et al. JAMA 312:1552, 2014.

Highlights of Modern Vancomycin Dosing for MRSA Infections

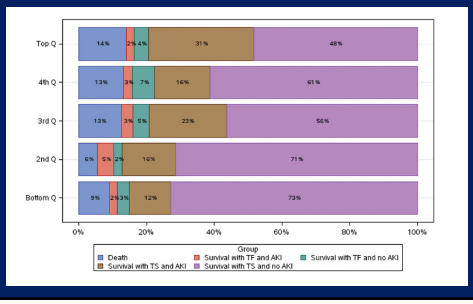
- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 (assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24
- Consider 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

Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

Lodise, et al Clinical Infectious Diseases 2020;70(8):1536–45

>757
621-757
516-621
390-516
< 389



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AHA guidelines for therapy of native valve S. aureus endocarditis

- MSSA
  - Nafcillin (or Oxacillin) 2 gm q4h x 6 weeks
  - Cefazolin 2 gm q8h x 6 weeks, allergic or intolerant to naf
  - No aminoglycoside
- MRSA
  - Vancomycin 30-60 mg/kg/d divided q8-12h to achieve trough of 15-20 µg/ml x 6 weeks
  - Daptomycin 6-10 mg/kg q24h x 6 weeks
  - No aminoglycoside

Circulation. 2015 Oct 13;132(15):1435-86

Duration of Therapy of *S. aureus* Bacteremia

Outcomes of *S. aureus* Bacteremia 2 weeks or >2 weeks

Category, N (Days of Rx, IQR)	Outcome		
	Success	Clinical Failure#	Non-evaluable
Uncomplicated, 59 (14-17 days)	73%	15%	11%
Complicated, 37 (17-33 days)	65%	27%	8%

*#Change in Rx, new infection, relapse/persistent bacteremia, death

Holland, et al. JAMA 2018;320:1249

Outcomes of Uncomplicated S. aureus Bacteremia: 14 days vs. >14 days

Outcomes	14 day Rx (n=21)	> 14 days Rx (n=43)
Death due to SAB	0	0
Relapse	0	2 (5%)
All cause mortality	2 (10%)	2 (5%)
Catheter-associated AE	0	7 (16%)
Adverse drug event	5 (24%)	7 (16%)

Taupin, OFID. 2020; 2020 Sep 29;7(10):ofaa457. doi: 10.1093/ofid/ofaa457

How common is uncomplicated *S. aureus* Bacteremia?

Study	# eligible	# screened
Taupin	64 (10.4%)	612
14 day Rx	21	
>14 day Rx	43	
Holland (RCT)	116 (1.9%)	~6000*
Uncomplicated SAB	79	
Complicated SAB	37	

*Known or suspected complicated SAB at screening was an exclusion

Duration of Therapy for S. aureus BSI

14 days
- UNCOMPLICATED (uncommon)
- Fever resolves by day 3
- Sterile blood culture after 2-3 days (DOCUMENT!)
- Easily removed focus of infection (no DVT)
- No metastatic infection (e.g., osteo)
- Negative echo, no evidence of endocarditis
- No predisposing valvular abnormalities
- (No implanted prosthetic devices, no DM, no immunosuppression)

4-6 weeks +
- COMPLICATED (usually is)
- 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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Combination Therapy of S. aureus BSI

Q5. 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

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	1 d 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

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Dapto + fosfomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Consider for salvage therapy, not first line

Once bacteremia clears on a combo salvage regimen, mono or combo follow-on?

263 patients, NVE, osteo, brain abscess (1), ≥4 d MRSA + BC

↓

80 patients, vanco/dapto + ceftaroline

↓

30 evaluable patients
15 combo
15 mono

Outcome	Mono	Combo
AKI	6	7
Leukopenia	0	1
Recurrence	1	0
Readmission	2	0
Death	1	3

Infect Dis Ther (2020) 9:77–87

Monotherapy versus combination therapy for *Staph. aureus* bacteremia

- No high quality RCT has demonstrated improved mortality with combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are mostly low quality, retrospective, subject to bias, and based on subjective outcomes (e.g., change in therapy) not mortality, recurrence, metastatic infections*
- Reserve for salvage therapy

Possible exception: Dapto + Fosfo vs Dapto, Pujol, et al. Clin Infect Dis 2021; 72:1517

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