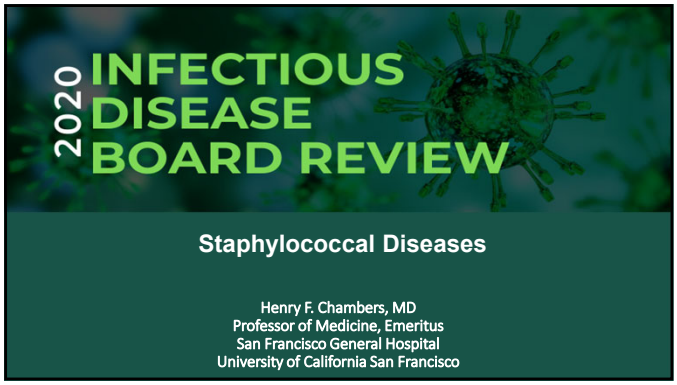
10 - Staphylococcal Diseases

Speaker: Henry Chambers, MD



Disclosures of Financial Relationships with Relevant Commercial Interests

- None

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 a slide-coagulase test 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

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

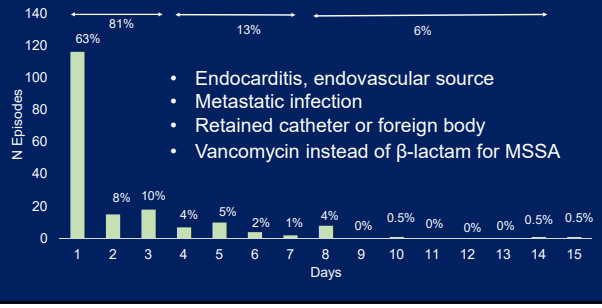
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

Clinical features of complicated Staph. aureus bacteremia

- Positive blood cultures >48-72h on therapy (Odds ratio = 5.6)
- Community-onset (OR 3.1)
- Fever > 3 days on therapy (OR 2.2)
- Skin findings c/w systemic infection (OR 2.0)
- Persistent or secondary focus of infection
- Endocarditis, prosthetic valve
- (Elderly patient: age > 60 years?)
- (MRSA?)

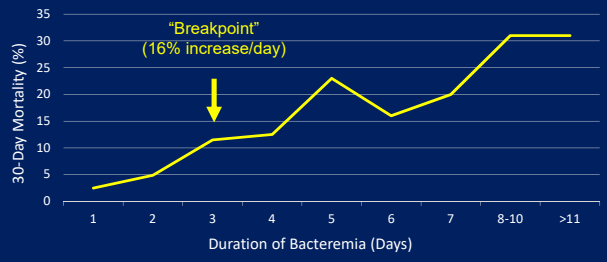
Adapted from Fowler, Ann Intern Med 163:2066, 2003

Duration of MRSA bacteremia on therapy San Francisco General 2008-12



- Endocarditis, endovascular source
- Metastatic infection
- Retained catheter or foreign body
- Vancomycin instead of β-lactam for MSSA

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]

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]

Q3. In patients with S. aureus bacteremia follow-up blood cultures should be obtained until negative.

A. True
B. False

Duration of therapy for SAB

Duration	Indications
14 days	• Fever resolves by day 3 • Sterile blood culture after 2-3 days • Easily removed focus of infection • No metastatic infection (e.g., osteo) • Negative echo, no evidence of endocarditis • No predisposing valvular abnormalities • No implanted prosthetic devices • (No DM, immunosuppression)
4-6 weeks +	• Failure to meet one or more of above criteria • Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

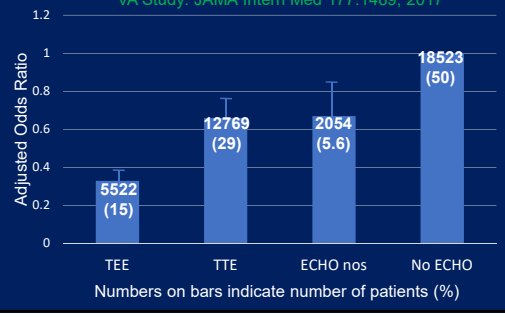
Echocardiography

Q4. For patients with Staph. aureus bacteremia which one of the following statements about echocardiography is true?

A. Echocardiography is not associated improved outcomes of patients with Staph. aureus bacteremia
B. Transesophageal ECHO should be obtained in all patients with S. aureus bacteremia
C. Transthoracic and transesophageal ECHOs have comparable sensitivities for diagnosis of Staph. aureus endocarditis
D. Transthoracic and transesophageal ECHOs have comparable specificities for diagnosis of Staph. aureus endocarditis

ECHO and mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



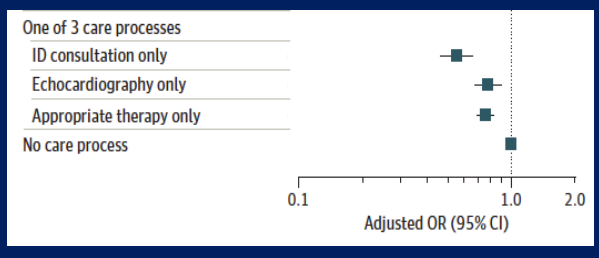
Role of echocardiography and what modality used for S. aureus bacteremia

Depends on the pre-test probability

- Consider TTE in all patients with SAB
  - Possible exception: HCA + no intracardiac devices + no signs IE + negative BC @ 48-72h
- Obtain TEE in high risk patients
  - Embolic events, intracardiac device, IVDU, prior IE

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

ID Consultation is Better than ECHO!



JAMA Intern Med 177:1489, 2017

Treatment of MSSA Bacteremia

Q5. 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.

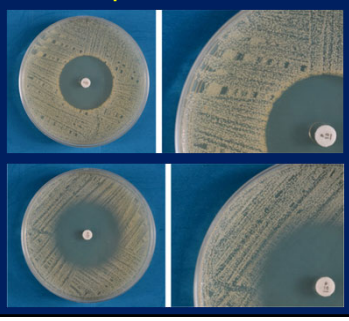
Pen MIC (µg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

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

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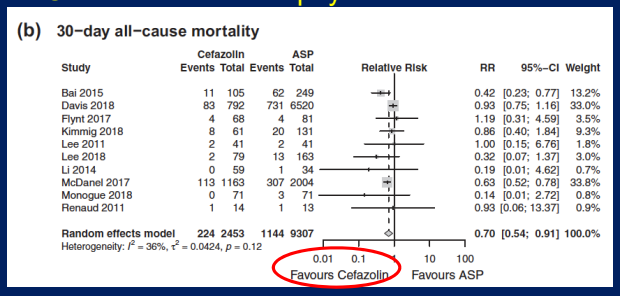
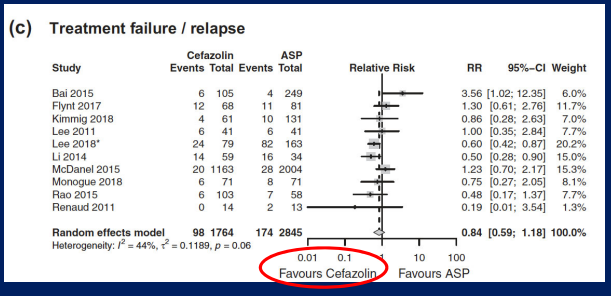
Cefazolin vs Anti-staphylococcal Penicillins



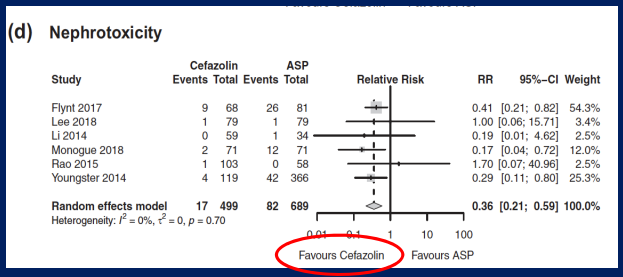
Weis, et al. / Clinical Microbiology and Infection 25 (2019):818e827

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

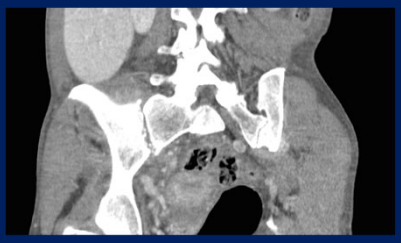
Q6. 36 year old female injection drug user with R hip pain, decreased ROM 2/2 pain; 2/2 blood cultures + for MSSA; CXR, right hip x-ray, CT abdomen and pelvis, MRI, TTE all normal. Treated with empirical vancomycin, blood cultures sterile after 1 day of therapy, now on day 5 of nafcillin. Pain much improved on day 7, but she still uses a cane for ambulation. **Which one of the following antibiotics would you recommend for a 6 week course?**

A. Dalbavancin
B. Ceftriaxone
C. Vancomycin
D. Cefazolin

What about ceftriaxone for MSSA bacteremia?

- Mixed data, low quality studies
- Open Forum Infect Dis. 2018 May 18;5(5):ofy089
  - Single VA medical center
  - 38 cefazolin and 33 with ceftriaxone.
  - Failure rates: 54.5% ceftriaxone versus 28.9% cefazolin; *P* = .029
- Avoid

Two months later….



Aspirate of R SI joint positive for MSSA

Lessons from this Case

- Community-onset is a risk factor for complicated bacteremia
- For the patient with suspected complicated infection, no evident focus, continued symptoms/+ blood cultures
  - Look harder, studies to consider
    - Repeat ECHO
    - MRI (may be false negative in early disease)
    - CT abdomen, pelvis,
    - PET-CT (J Nucl Med. 2018 Dec 14. pii: jnumed.118.221929)
    - Ultrasound to rule out septic thrombophlebitis

Tricky, occult foci of infections

- Spine, psoas muscle
- Fibrous/ligamentous joints: acromioclavicular, manubriosternal, sacroiliac, symphysis pubis
- Deep venous septic thrombosis

Summary: MSSA bacteremia

- Cefazolin is better tolerated than ASPs
- Recommended by AHA 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

Treatment of MRSA Bacteremia

Q7. 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

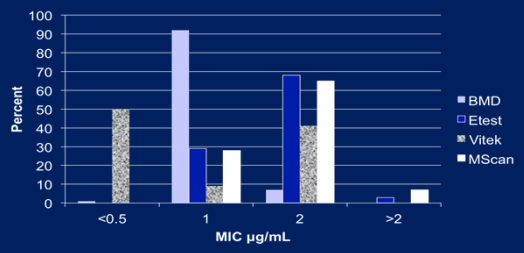
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr ≤ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic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

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 by Method



Int J Antimicro Agent 32:378, 2008

Original Investigation

Association Between Vancomycin Minimum Inhibitory Concentration and Mortality Among Patients With *Staphylococcus aureus* Bloodstream Infections
A Systematic Review and Meta-analysis

Andre C. Kalil, MD, MPH; Trevor C. Van Schooneveld, MD; Paul D. Fey, PhD; Mark E. Rupp, MD

- 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, JAMA 312:1552, 2014.

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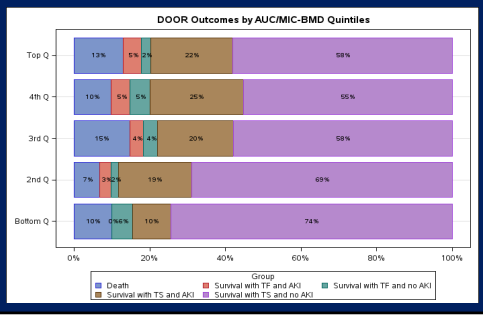
But what about that vancomycin MIC of 2 µg/ml?

- Vancomycin MIC = 1.5 to 2 µg/ml not a reliable predictor of clinical failure and not a reason to alter therapy
- Vancomycin MIC > 2 µg/ml is a reliable predictor of nonsusceptibility and clinical failure and another agent should be used

Vancomycin Dosing: AUC/MIC Correlates Poorly with Outcome

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

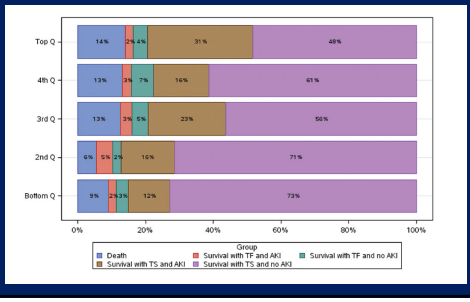
>1019
687-1018
563-686
421-562
< 421



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



Therapeutic monitoring of vancomycin for serious methicillin-resistant *Staphylococcus aureus* infections: A revised consensus guideline and review by the American Society of Health-System Pharmacists, the Infectious Diseases Society of America, the Pediatric Infectious Diseases Society, and the Society of Infectious Diseases Pharmacists

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

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

MRSA Decolonization

- Randomized controlled trial of education versus education + decolonization in hospitalized MRSA colonized adults
- Decolonization regimen: 5 days twice monthly of 4% chlorhexidine shower/bath + 0.12% chlorhexidine mouthwash 2x daily + 2% nasal mupirocin 2x daily
- MRSA infection 98/1063 (9.2%, ed) vs 67/1053 (6.3%, decolon) (p=0.015)
- Lower MRSA infection with decolonization: HR 0.70 (95% CI, 0.52-0.96)
- Lower risk of MRSA hospitalization: HR 0.71 (95% CI, 0.51-0.99)
- MRSA infection adherent vs education only: HR 0.56 (95% CI 0.36-0.86)

NEJM 2019;380:638-50

Combination Therapy of S. aureus Bacteremia

Q8. Which one of the following combinations have been shown to improve outcome of patients with S. aureus bacteremia or native valve endocarditis?

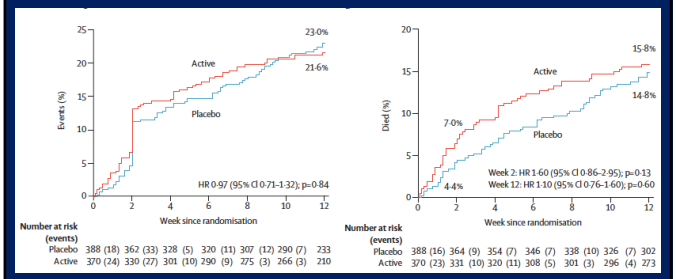
A. Anti-staphylococcal beta-lactam + gentamicin for MSSA
B. Anti-staphylococcal beta-lactam + rifampin for MSSA
C. Vancomycin + a beta-lactam for MRSA or MSSA, pending cultures
D. No combination regimen

Adjunctive rifampicin for *Staphylococcus aureus* bacteraemia (ARREST): a multicentre, randomised, double-blind, placebo-controlled trial

*Guy E Thwaites, Matthew Scarborough, Alexander Szubert, Emmanuel Nsutebu, Robert Tilley, Julia Greig, Sarah A Wyllie, Peter Wilson, Cressida Auckland, Janet Cairns, Denise Ward, Pankaj Lal, Achyut Guleri, Neil Jenkins, Julian Sutton, Martin Wiselka, Gonzalez-Ruiz Armando, Clive Graham, Paul R Chadwick, Gavin Barlow, N Claire Gordon, Bernadette Young, Sarah Meisner, Paul McWhinney, David A Price, David Harvey, Deepa Nayar, Dakshika Jeyaratnam, Tim Planche, Jane Minton, Fleur Hudson, Susan Hopkins, John Williams, M Estee Török, Martin J Llewelyn, Jonathan D Edgeworth, A Sarah Walker, on behalf of the United Kingdom Clinical Infection Research Group (UKCIRG)**

- 758 patients, 388 SOC and 370 SOC + rifampin
  - 40% deep tissue, 30% diabetics, 1y% IVDU, 6% MRSA, Mean of 62h pre-randomization antibiotics
- Primary outcome composite of treatment failure, recurrence, death at 12 weeks

Lancet. 2017 Dec 14. pii: S0140-6736(17)32456-X.
doi: 10.1016/S0140-6736(17)32456-X.



Composite Primary Outcome Death

CAMERA2

JAMA | Original Investigation

Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia
A Randomized Clinical Trial

Tong, et al. JAMA. 2020;323(6):527-537. doi:10.1001/jama.2020.0103

CAMERA2

- IV vancomycin (n=337) or daptomycin (n=8) (standard therapy) Vs. standard therapy plus 7 days of an anti-staphylococcal β-lactam (flucloxacillin, cloxacillin, or cefazolin [n=27]).
- Composite primary endpoint at 90 days of (1) all-cause mortality, (2) persistent bacteremia at day 5 or beyond, (3) microbiological relapse, or (4) microbiological treatment failure
- Target enrollment 440, 358 enrolled, study terminated by DSMB

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CAMERA2

Outcome	Standard Therapy	Combination Therapy	Risk Difference (95% CI)
Primary	68/175 (39%)	59/175 (35%)	−4.2 (−14.3 to 6.0)
90 day mortality	28/174 (16%)	35/170 (21%)	4.5 (−3.7 to 12.7)
+ BC @ day 5	35/172 (20%)	19/166 (11%)	−8.9 (−16.6 to −1.2)
Relapse	18/175 (10%)	14/169 (8%)	-2.0 (−8.1 to 4.1)
Treatment failure	17/175 (10%)	16/170 (9%)	−0.3 (−6.5 to 5.9)
AKI	9/145 (6%)	34/145 (23%)	17.2 (9.3 to 25.2)

Daptomycin + Ceftaroline

Clinical Data on Daptomycin plus Ceftaroline versus Standard of Care Monotherapy in the Treatment of Methicillin-Resistant *Staphylococcus aureus* Bacteremia

Geriak, et al. Antimicrob Agents Chemother. 2019; 63:e02483

Is Daptomycin plus Ceftaroline Associated with Better Clinical Outcomes than Standard of Care Monotherapy for *Staphylococcus aureus* Bacteremia?

Kalil, et al. Antimicrob Agents Chemother. 2019; 63:e00900

Reply to Kalil et al., "Is Daptomycin plus Ceftaroline Associated with Better Clinical Outcomes than Standard of Care Monotherapy for *Staphylococcus aureus* Bacteremia?"

Sakoulas, et al. Antimicrob Agents Chemother. 2019; 63:e01347

Daptomycin + Ceftaroline

Consider for salvage therapy, not first line

Clinical Data on Daptomycin plus Ceftaroline ver… of Care Monotherapy in the Treatment of M… sistant *Staphylococcus aureus* Bacteremia

Geriak, et al. Antimicrob Agents Ch… 63

Is Daptomycin plus Ceftar… ted with Better Clinical Outcomes than Stand… Monotherapy for *Staphylococcus* …eremia?

…icrob Agents Chemother. 2019; 63:e00900

R… et al., "Is Daptomycin plus Ceftaroline …d with Better Clinical Outcomes than Standard of …e Monotherapy for *Staphylococcus aureus* Bacteremia?"

Sakoulas, et al. Antimicrob Agents Chemother. 2019; 63:e01347

Monotherapy versus combination therapy for Staph. aureus bacteremia

- No high quality RCT has ever demonstrated improved outcomes of combination antimicrobial therapy over monotherapy
- Studies suggesting a possible benefit of combination therapy are low quality, retrospective, and based on subjective outcomes not mortality, recurrence, metastatic infections

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