Staphylococcal Infection - Bacteremia

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Disclosures of Financial Relationships with Relevant Commercial Interests

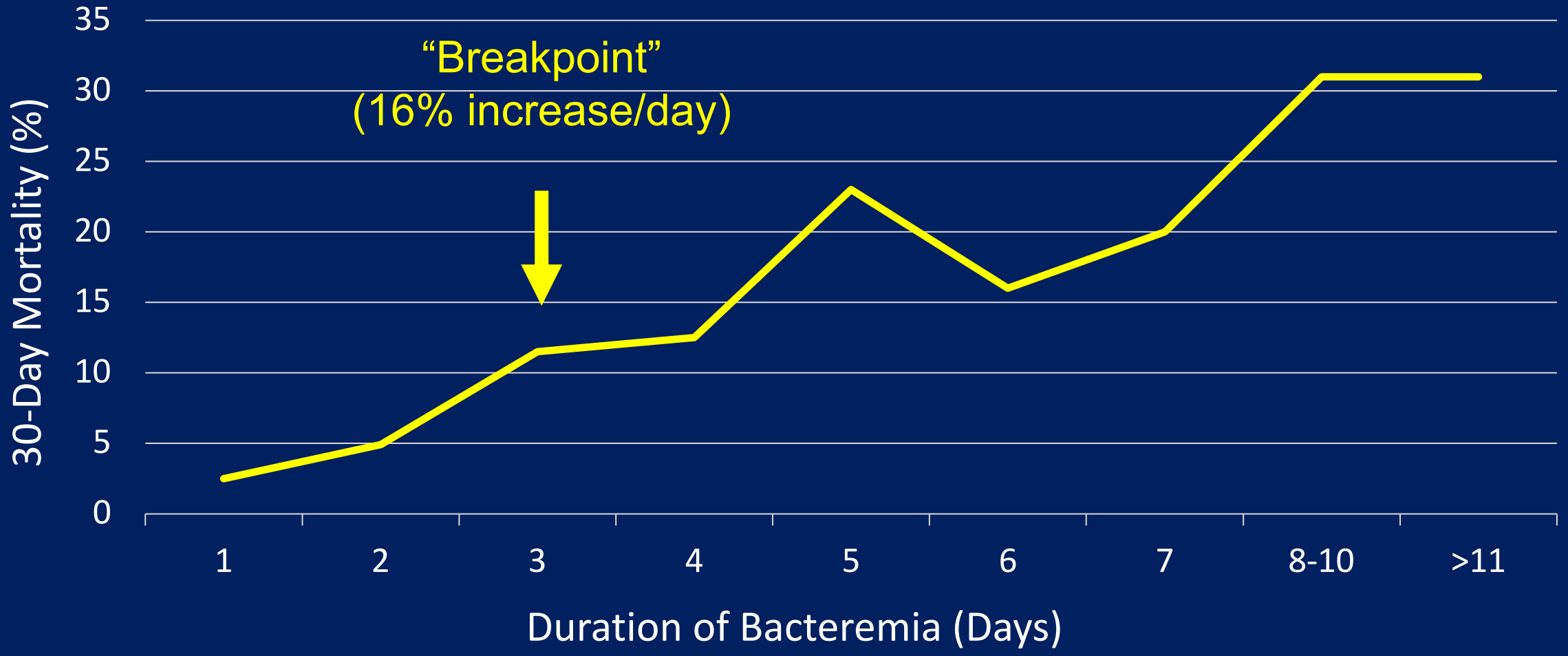
Moderna – Stock
Merck – Data Monitoring Committee, Stock
Janssen – Consultant

Outline of the Talk

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

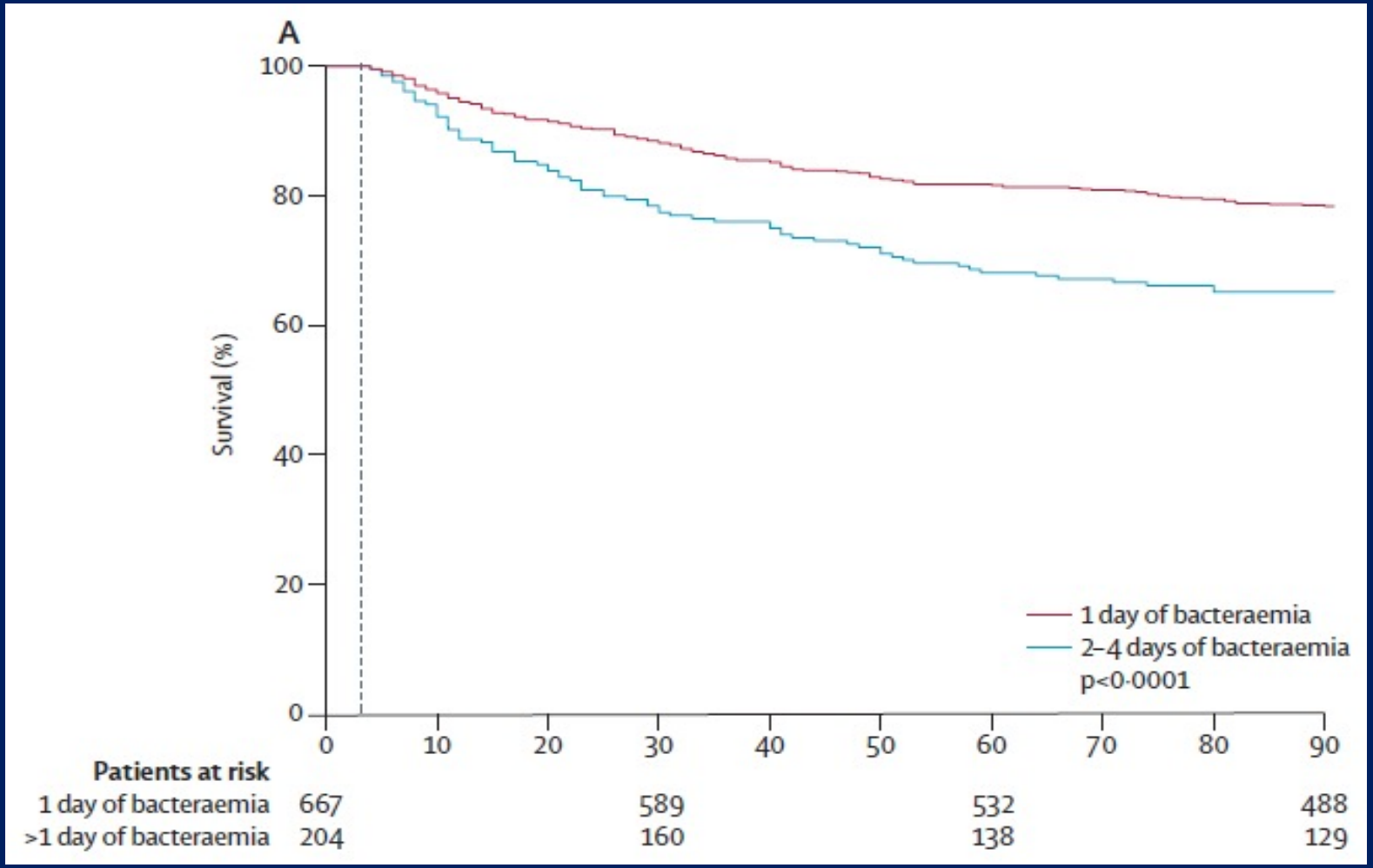
Risk factors for poor outcome, complicated S. aureus bacteremia

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



Clin Infect Dis. 2020; 70:566-573

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. 2020; 70:566-573

Uncomplicated vs Complicated Bacteremia

- UNCOMPLICATED (~ 1/3 of patients)
- 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)

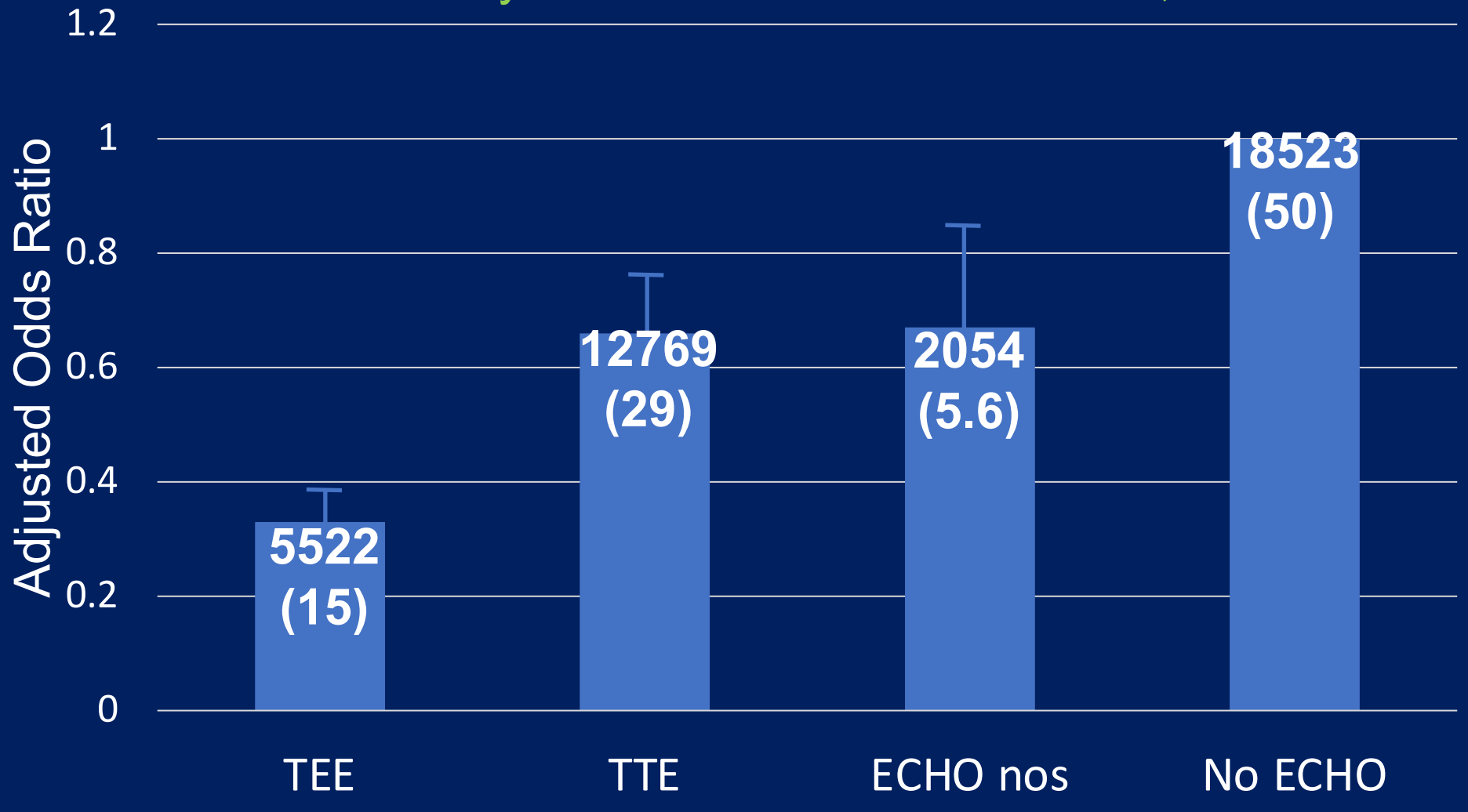
- COMPLICATED (~ 2/3 of patients)
- Failure to meet one or more of above criteria
- Osteomyelitis, endocarditis, epidural abscess, septic arthritis, pneumonia, complicated UTI

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

Echocardiography

ECHO and mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

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

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 2015; 61:361

Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

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

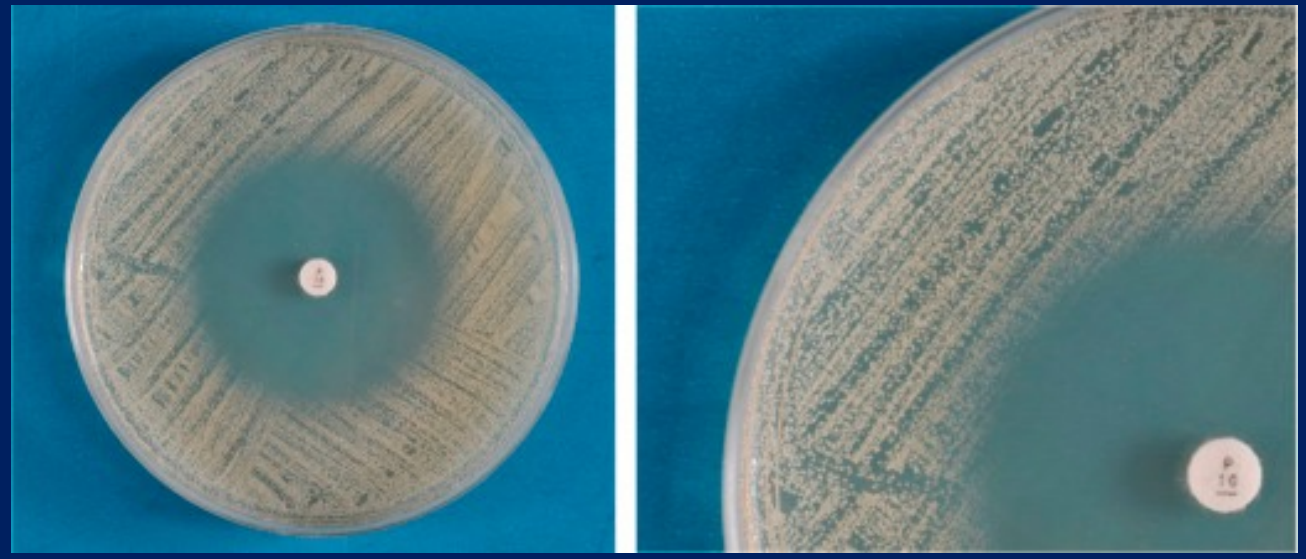
Pen MIC (µg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

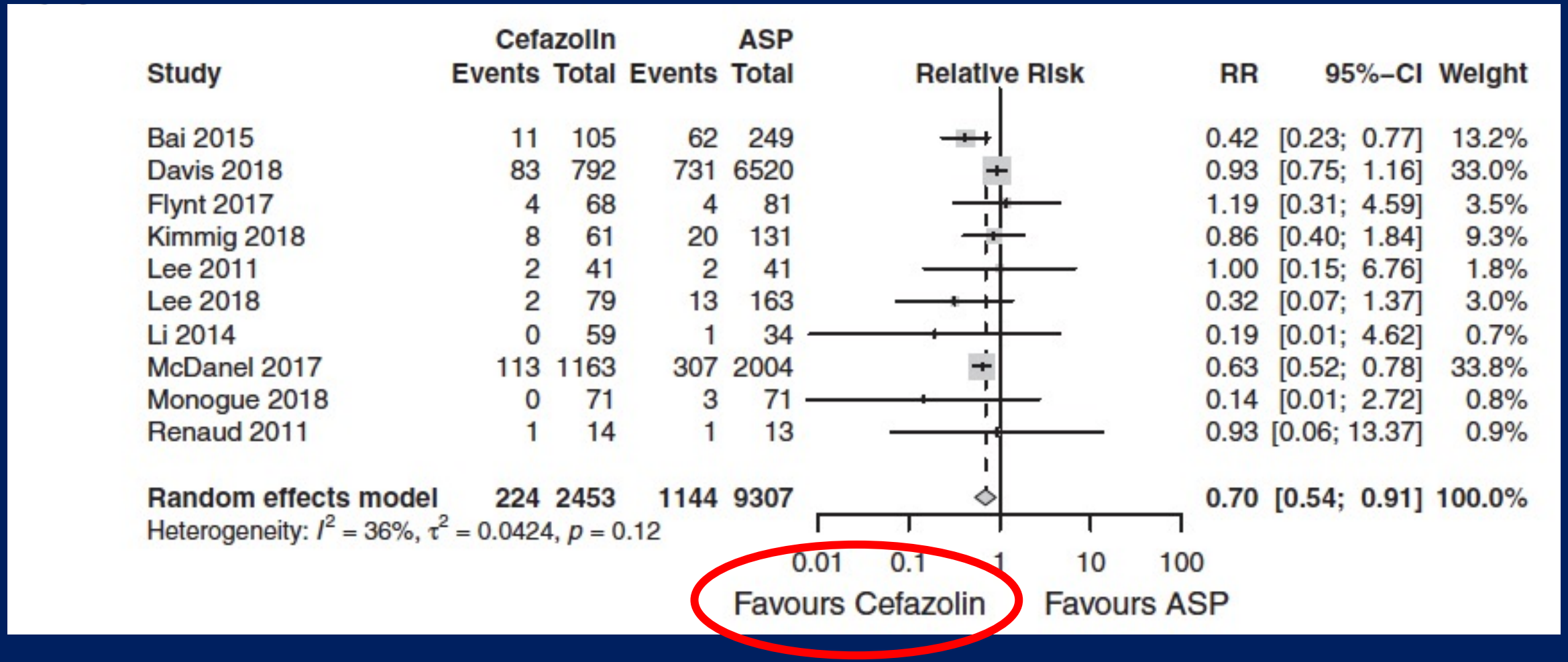
Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins (ASP)

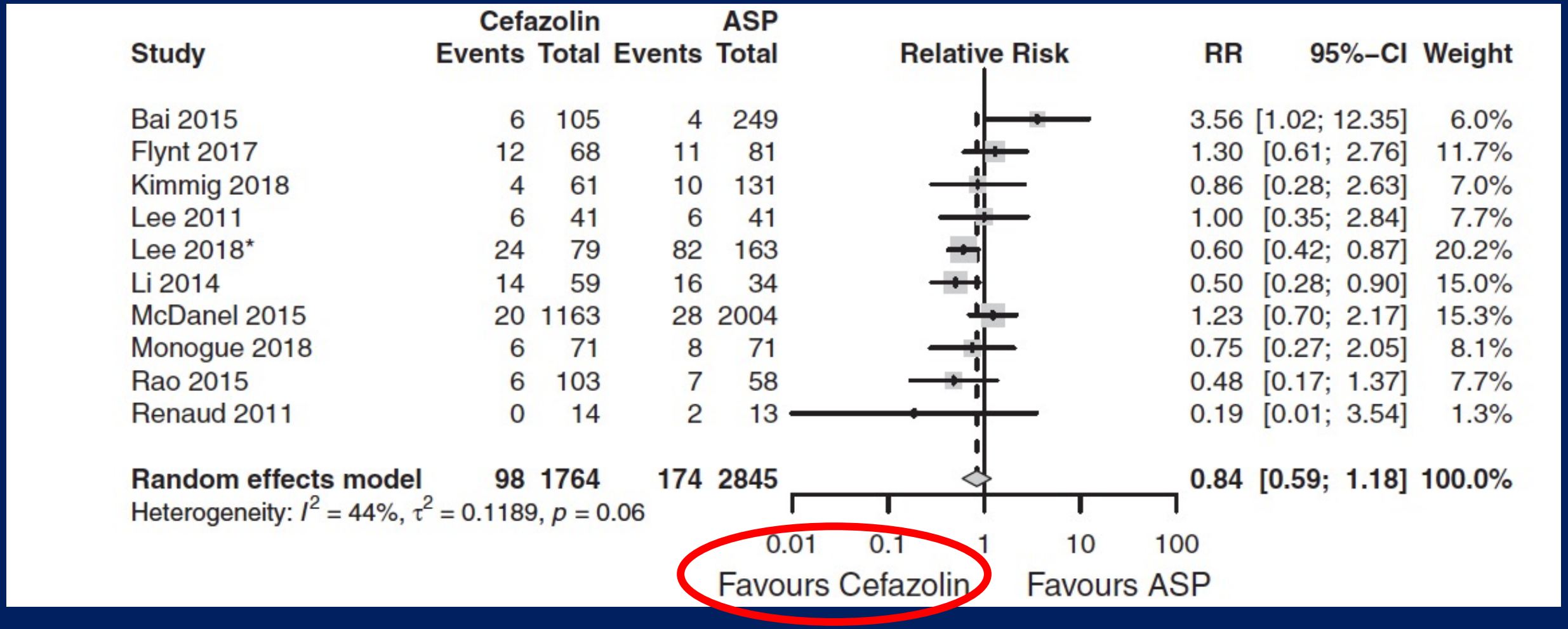
- Efficacy:
  - Penicillinase inoculum effect on cefazolin MICs – does it matter?
- Safety :
  - Adverse events due to ASPs

Mortality: Cefazolin vs ASP



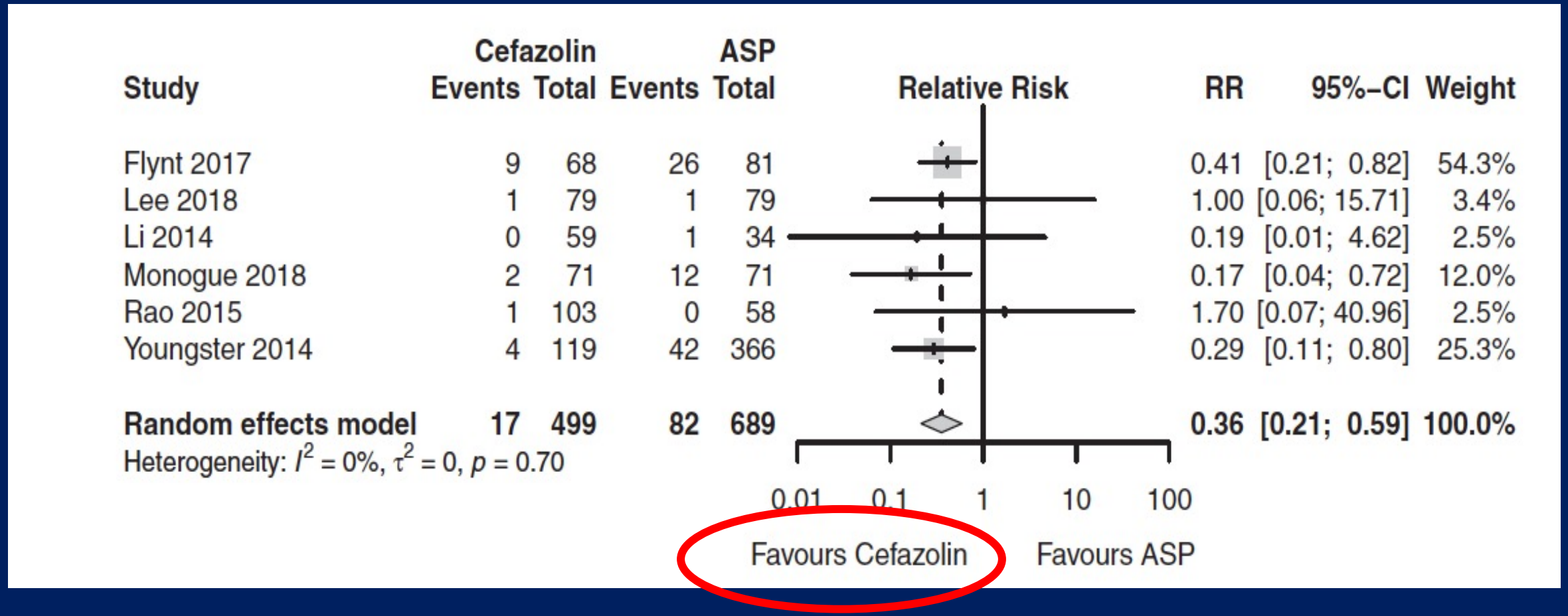
Weis, et al. Clin Microbiol Infect 2019; 25:818

Treatment Failure/Relapse: Cefazolin vs ASP



Weis, et al. Clin Microbiol Infect 2019; 25:818

Nephrotoxicity: Cefazolin vs ASP



Weis, et al. Clin Microbiol Infect 2019; 25:818

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

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

- ASP and cefazolin are first line, ASP preferred at least initially
- 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

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

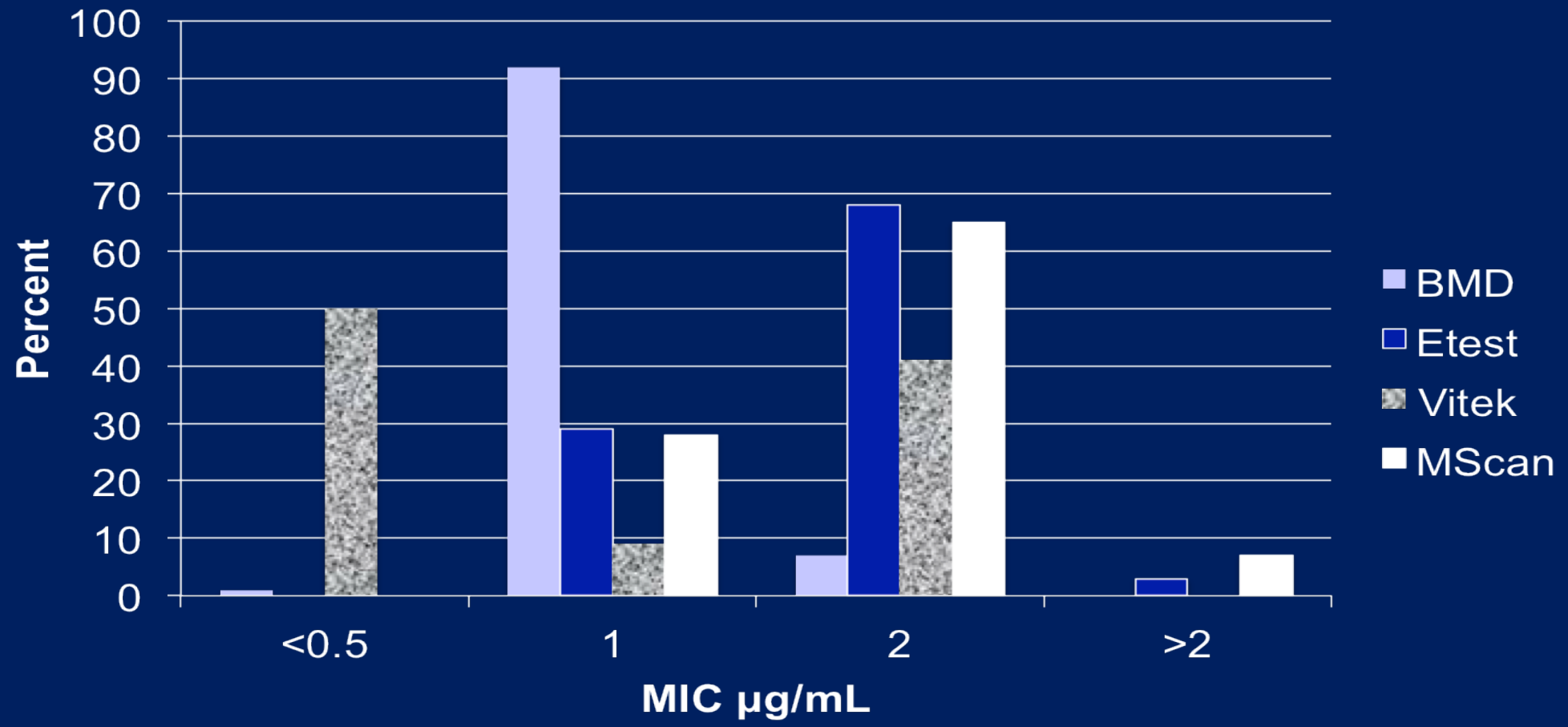
Antibiotic	Indications	Comments
Linezolid	SSTI, HAP, VAP	Serotonin syndrome: avoid use with SSRIs, MAO-Is; bacteriostatic Bone marrow suppression
Telavancin	SSTI, HAP, VAP	Vancomycin derivative Nephrotoxic, black box warning for ClCr $\leq$ 50 ml/min Artificially prolongs PT, PTT QTc prolongation, teratogenic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

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 a 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 2014; 312:1552.

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

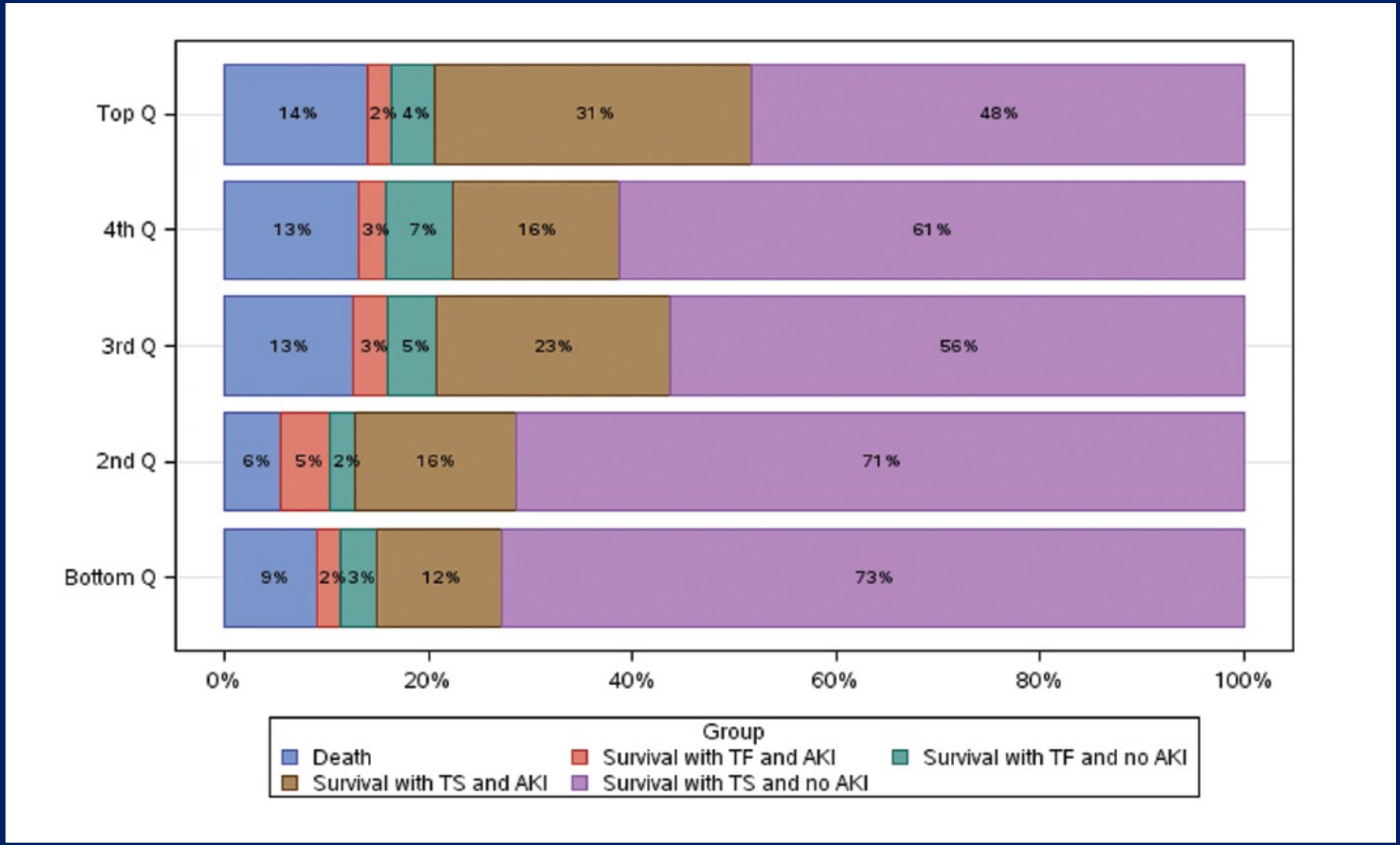
>757

621-757

516-621

390-516

< 389



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

Oral Therapy of S. aureus Bacteremia

Recent Studies of Oral Therapy - 1

PMID	Study Design	SAB Populaiton	Oral Agents	Median Duration	Relapse/ Clinical Failure	Mortality
33606007 CID 2021	Retrospective cohort Single center	Comp 96% MSSA No endovascular infection, neg PET-CT, neg ECHO 45 IV 61 PO Switch	Clindamycin	IV: 45 days PO: 44 days	IV: 0 PO: 0	IV: 13.3% PO: 7%
33157291 IJID 2021	Retrospective cohort Single center	Comp (n=75) Uncomp (n=126) 18% MRSA 76 IV 125 PO Switch	T/S (66%) FQ (18%) Linezolid (9%)	IV: 22 days PO: 25 days	IV: 6% PO: 3%	IV: 16% PO: 7%

Recent Studies of Oral Therapy - 2

PMID	Study Design	SAB Populaiton	Oral Agents	Median Duration	Relapse/ Clinical Failure	Mortality
32015029 AAC 2020	Retrospective cohort Single center	Uncomplicated 95% MSSA 16 IV 84 PO	Fluclox: 71% Cephalexin: 8% T/S, Clinda: 10%	IV: 16 d PO: 14 d	IV: 6% PO: 4%	IV: 6% PO: 2%
30418557 JAC 2019	Retrospective cohort Single center	Comp (n=320) Uncomp (n=172) 100% MRSA 422 IV 70 PO Switch	Linezolid (50%) T/S (34%) Clinda (11%)	IV: 35 d PO: 21 d	IV: 14.9% PO: 7.1%	IV: 5.5% PO: 1.4%
30351401 CID 2019	Prospective cohort Single center	Low Risk 16% MRSA 107 IV 45 PO	Linezolid	IV: 15 d PO: 15 d	IV: 3.7% PO: 2.2%	IV: 15.9% PO: 2.2%

Summary: Oral therapy of S. aureus Bacteremia

- Quality of studies is low, subject to selection bias, confounding by indication
  - Relapse rates consistently higher with IV
  - Mortality rates consistently higher with IV
- Avoid for treatment of endocarditis, endovascular infections, complicated bacteremia
- May be an option for treatment of uncomplicated bacteremia in carefully selected patients, but there is a lack of standard definition
- ID consultation strongly recommended
- Prefer agents with good oral bioavailability: linezolid, T/S, FQ+rif, clindamycin (?), anti-staphylococcal beta-lactam (?)

See Dagher, et al. Open Forum Infect Dis 2020 May 5;7(6):ofaa151.

Duration of Therapy of *S. aureus* Bacteremia

Duration of Therapy for S. aureus BSI

14 days

- UNCOMPLICATED
- 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
- 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

Duration of Therapy (DOT) and Outcome of SAB

- Retrospective cohort study, single center
  - 530 patients: 305 complicated, 225 uncomplicated
  - 17.7% MRSA
- Compared two DOT “breakpoints”
  - ≤ 14 days v > 14 days
  - ≤ 21 days v > 21 days
- Key results
  - Relapse rates: 4.0 % vs 3.8% and 3.1% vs 3.6%, respectively
  - Mortality: 29.3% v 15.8% and 20.8% v 11.1%
  - DOT > 14 day associated with lower mortality for complicated bacteremia but not uncomplicated bacteremia
  - DOT > 21 days not associated with lower mortality for either type of bacteremia (but unadjusted HR 0.46 [0.23-0.93 for complicated])

Abbas, et al. Clin Microbiol Infect 2020; 26:626,
See also review by Eichenberger, et al. Clin Microbiol Infect. 2020 May ; 26(5): 536–538

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

Even Shorter Course Therapy For Low Risk SAB?

- Retrospective study of 1005 patients from 3 cohorts of patients with “low risk” MSSA bacteremia
- 6-10 days of treatment (SC) compared to 11-16 days (PC)
- PC patients had higher CRPs, more HA infections, more ECHOs, more PO therapy

Cohort (N)	Mortality		Relapse	
	SC	PC	SC	PC
I (645)	19.3%	19%	5.4%	8.4%
II (219)	23%	20.7%	--	--
III (141)	17.6%	20%	--	--

Thorlacius-Ussig, et al. 2021; Clin Infect Dis 73:866

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

Combination Therapy of S. aureus BSI

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

Overview of Studies of Combination Therapy for SAB

Regimen	Study	Population	Comments	
Adjunctive rifampin	RCT	MRSA, MSSA	No bene[illegible]	[illegible]9249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MS[illegible]	[illegible], toxic	Various
Adjunctive dapto	RCT		No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RC[illegible]	[illegible]SA	↑↑ AKI, higher mortality	32044943
Dapto + ceftar[illegible]	[illegible], aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Da[illegible]ostomycin	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

Thanks