21 – Staphylococcal Disease

Speaker: Henry F. Chambers, MD

IDBR INFECTIOUS DISEASE BOARD REVIEW AUGUST 20-24 2022

Staphylococcal Diseases

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7/11/2022

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Disclosures of Financial Relationships with Relevant Commercial Interests

- **Stock: Moderna**
- **Stock: Merck**
- **Data Monitoring Committee: Merck**

Outline of the Talk

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

IDBR INFECTIOUS DISEASE BOARD REVIEW 2022 PREVIEW QUESTION

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 (5-10% *mecA* positive)

Risk factors for poor outcome, complicated S. aureus bacteremia

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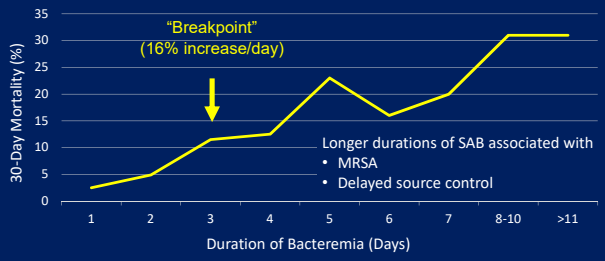
Q2. Which one of the following risk factors is most predictive of complicated Staph. aureus bacteremia?

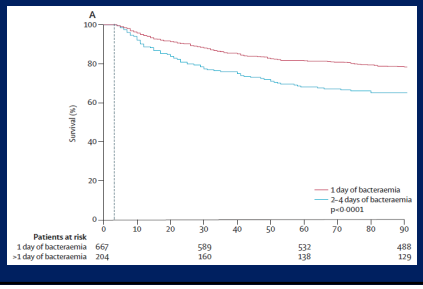
A. MRSA infection
B. Hospital-onset infection
C. Positive blood cultures on appropriate therapy
D. Community-onset infection

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



Clin Infect Dis. 2020; 70:566-573

Even 2 days of Bacteremia on Therapy is Bad



Lancet Infect Dis 2020; 20: 1409

Echocardiography

Q3. 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

Prediction Scores to Rule Endocar… (and avoid an ECHO…

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

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

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

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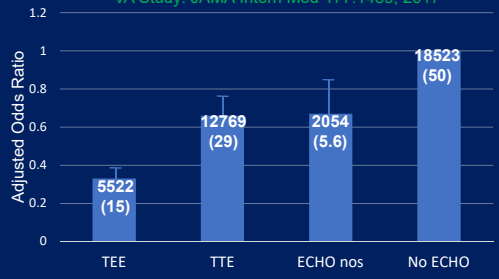
ECHO and Mortality in S. aureus Bacteremia

VA Study: JAMA Intern Med 177:1489, 2017



Numbers on bars indicate number of patients (%)

Role of Echocardiography for S. aureus Bacteremia

- Prevalence of endocarditis 12%-18% overall
- Depends on the pre-test probability
  - 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

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

Treatment of MSSA Bacteremia

IDSA 2022 PREVIEW QUESTION

Q4. 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**

Tolerability of Cefazolin in Nafcillin-Intolerant Patients for the Treatment of Methicillin-Susceptible *Staphylococcus aureus* Infections

Ankit M. Gandhi,[1,2] Megan D. Shah,[1] Lindsay E. Donohue,[1] Heather L. Cox,[1] and Joshua C. Eby[3]

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Clinical Infectious Diseases 2021;73(9):1650

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Penicillin for treatment of Staph. aureus endocarditis per AHA guidelines

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

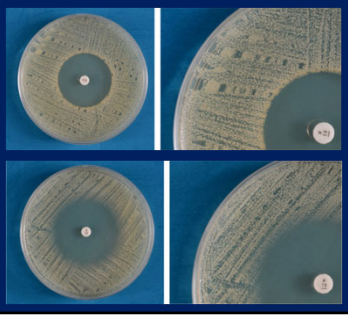
Pen MIC (µg/ml)	No. (%) of strains	
	Tested for blaZ	PCR + for blaZ
0.015	1 (100)	0
0.03	24 (100)	0
0.06	370 (100)	14 (3.4)
0.12	53 (100)	17 (32.1)

J Clin Micro 54:812, 2016

Zone edge test for β-lactamase

Positive

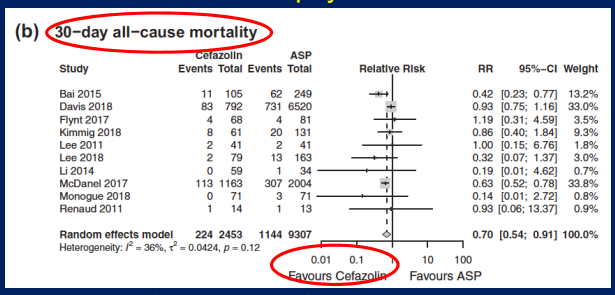
Negative



MSSA Bacteremia: Cefazolin vs. Antistaphylococcal Penicillins

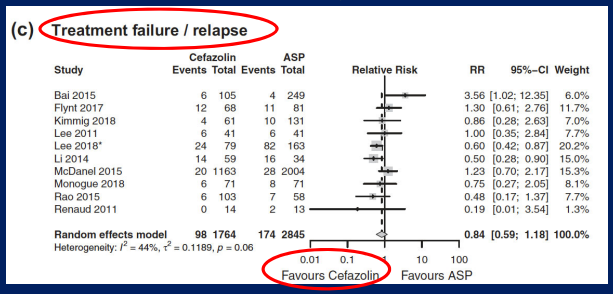
- Efficacy:
  - Penicillinase inoculum effect on cefazolin MICs – does it matter?
- Safety :
  - Adverse events due to ASPs

Cefazolin vs Anti-staphylococcal Penicillins



Clinical Microbiology and Infection 25 (2019):818e827

Cefazolin vs Anti-staphylococcal Penicillins



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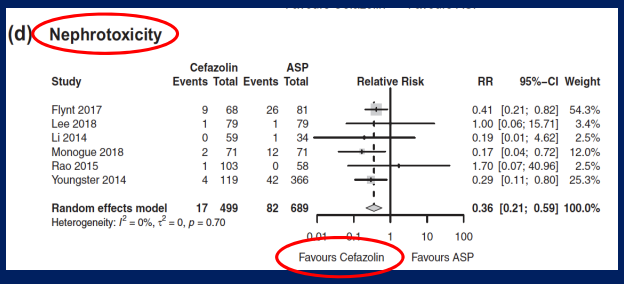
Cefazolin vs Anti-staphylococcal Penicillins



Clinical Microbiology and Infection 25 (2019):818e827

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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

AHA Guidelines for S. aureus Native Valve 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
  - Daptomycin 6-10 mg/kg q24h x 6 weeks
  - No aminoglycoside

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

What about Ceftriaxone for MSSA Bacteremia?

- Meta-analysis of 12 retrospective cohort studies comparing ceftriaxone (n=1037) to SOC (n=2088)
- No significant difference in
  - Clinical cure rates
  - Microbiological cure rates
  - 30-day or 90-day mortality
  - 90-day readmission
  - Adverse drug reactions
- Caveats: patients in SOC were sicker, had more severe disease, endovascular infections, doses not well defined

Antibiotics 2022, 11:375

Summary: MSSA bacteremia

- Prefer a beta-lactam
- ASPs first drug of choice, but Cefazolin is better tolerated than ASPs
  - AHA second-line agent for native valve endocarditis
  - Overall mortality no worse, may be better 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
- Avoid vancomycin, daptomycin if you must (ref below**)
- Ceftriaxone may be efficacious in selected patients, avoid for endocarditis, probably not a good answer on the boards

**Intern J Antimicrobial Agents 2021; 58:106363

Treatment of MRSA Bacteremia

2022 PREVIEW QUESTION

Q5. 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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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 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
  - Some cross-resistance with VISA

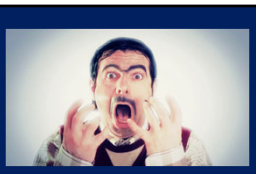
Holland et al: JAMA 312:1330, 2014

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

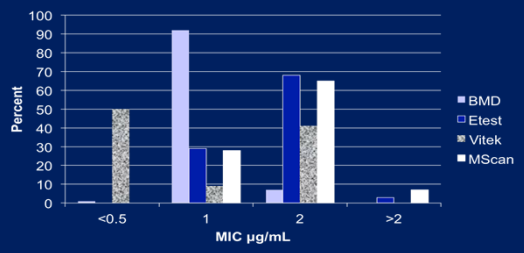
FDA-approved antibiotics for MRSA Infections

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 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.

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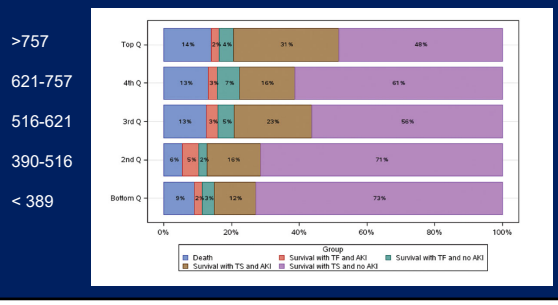
Vancomycin Dosing: Higher AUC Correlates with Worse Outcome

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



Highlights of Modern Vancomycin Dosing for MRSA Infections

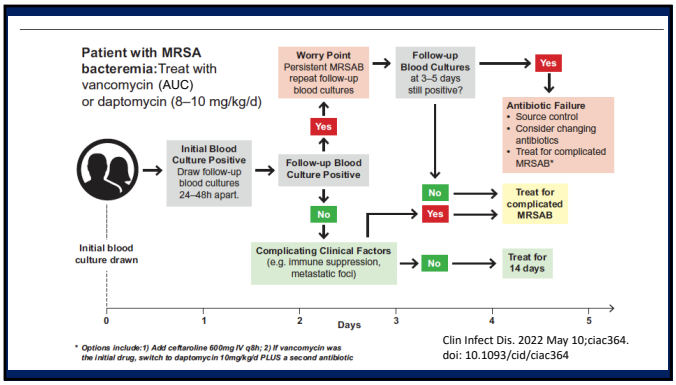
- Use of troughs no longer recommended
- Target AUC/MIC_{MBD} to 400-600 mg*h/L(assume MIC_{BMD} = 1 μg/ml)
  - Bayesian-derived monitoring, 1-2 samples (Cmax, Cmin)
  - 1st order PK equation with C_{max}, C_{min} at near steady-state
  - Continuous infusion: multiply steady-state concentration x 24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

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~~ AUC 400-600 x 6 weeks
  - Daptomycin 6-10 mg/kg q24h x 6 weeks
  - No aminoglycoside

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



Clin Infect Dis. 2022 May 10;ciac364. doi: 10.1093/cid/ciac364

Duration of Therapy for S. aureus BSI

14 days

- UNCOMPLICATED (~10% of cases)
- 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

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
- Role in treatment of and efficacy for endocarditis, endovascular infections, complicated bacteremia not well defined
- 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.

Combination Therapy of S. aureus BSI

Q6. 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 S^B

Regimen	Study	Population	Comments	
Adjunctive rifampin	RCT	MRSA, MSSA	No benef	29249276
Adjunctive aminoglycoside	Obs., RCT	MRSA, MSS	, toxic	Various
Adjunctive dapto	RCT		No benefit	32667982
Adjunctive β-lactam + vanco/dapto	RCT	A	↑↑ AKI, higher mortality	32044943
Dapto + ceftar	aborted RCT	MRSA	Low quality data	30858203, 31640977, 31404468
Da stomycin	RCT	MRSA	No mortality benefit, ↓ micro failure, ↑ AEs	32725216 32887985

Consider for salvage therapy, not first line

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

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

- Single center, retrospective study, 146 patients, ≥72h of dapto + ceftaroline combo
  - Combo: 66 on combo ≥ 10 days (IQR 13-21 days)
  - Mono: 74 on combo < 10 days (IQR 4-6 days)
    - De-escalated to dapto (n=30), ceftaroline (n=18), or vanco (n=26)
- Days of therapy prior to dapto + ceftaroline
  - Combo: 6 (IQR 4-9)
  - Mono: 7 (IQR 5-11)

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

De-Escalation of Combo Therapy for Complicated MRSA bacteremia

Outcome	Combo (n=66)	Mono (n=74)	P-value
Composite clinical failure	14 (21%)	8 (24%)	0.66
Recurrent bacteremia, 60d	2 (3%)	5 (7%)	0.45
In-patient mortality	1 (2%)	4 (5%)	1
Readmission, 60d	13 (20%)	13 (18%)	0.75
Duration of bacteremia, d	8 (IQR 6-11)	8 (IQR 5-12)	0.33
Adverse drug event	2 (4%)	1 (1)	0.47
Length of stay, d	26 (IQR 20-41)	24 (IQR 16-33)	0.08

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

Thanks

Back-Up Slides

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)
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- 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

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

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

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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

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 short-course (SC) treatment vs 11-16 days, prolonged course (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

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%

De-Escalation of Combo Therapy

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

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

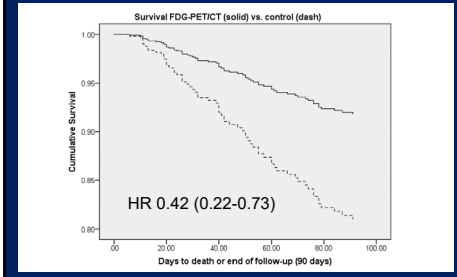
Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia

Detection of Infected Foci by PET/CT according to Clinically Suspicion

Clinically suspected sites (n=136)		PET/CT + sites (n=179)	
PET/CT +, confirmed	72 (53%)	PET/CT +, clinically unsuspected	145 (69%)
PET/CT -, excluded	64 (47%)	PET/CT +, clinically suspected	72 (31%)

Clin Infect Dis. 2021;73:e3859

Matched Cohort Study of FDG-PET/CT in Patients with Staph. aureus Bacteremia



Issues:
--Availability
--Reimbursement
--Observation studies only

Clin Infect Dis. 2021;73:e3859