PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

It Isn't in My Blood: Unconventional Antibiotic Approaches for Staphylococcus aureus Bacteremia

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DISCLOSURE

- I have no potential conflict of interest

Learning Objectives

- Recognize first line treatment options for *Staphylococcus aureus* bacteremia and signs of treatment failure
- Describe how different combinations of antibiotic classes can be used to treat *Staphylococcus aureus* bacteremia
- Develop a complete workup and treatment regimen for patients with *Staphylococcus aureus* bacteremia

BACKGROUND

STAPHYLOCOCCUS AUREUS

- Gram-positive cocci forming grape-like clusters on gram stain
- Coagulase-positive staphylococci
  - Coagulase: a surface enzyme that converts fibrinogen to fibrin
- The most virulent of staphylococcal species
  - Surface proteins promoting colonization of host tissues
  - Factors inhibiting phagocytosis
  - Toxins damaging host tissues and causing disease symptoms
- Commensal and opportunistic pathogen

1. Harrison's Infectious Diseases. 3rd Edition
2. Medical Microbiology. 4th Edition.

EPIDEMIOLOGY

- One of the most common pathogens in healthcare facilities and in the community
- 2017: estimated 120,000 *S. aureus* bacteremia (SAB) with 20,000 associated deaths
  - 2005-2012: 17.1% decrease in methicillin-resistant *S. aureus* (MRSA) bloodstream infection rates from
    - 2013-2016: decline has slowed
- Hospital-onset methicillin-susceptible *S. aureus* (MSSA) infections not significantly changed
- 2012-2017: Community-onset MSSA infections increased 3.9% per year

3. https://www.cdc.gov/mmwr/volumes/68/wr/mm6809e1.htm

MORTALITY

- *S. aureus* bacteremia has mortality rates as high as 30-40%
- Complications include sepsis, endocarditis, vasculitis, and metastatic seeding (bones, joints, kidneys, lungs)
- Predictors of Mortality
  - Host factors
  - Pathogen-host interactions
  - Pathogen specific factors

1. Harrison's Infectious Diseases
4. *Ther Adv Infectious Dis.* 2019; 6:1-10
5. *Clin Microbiol Rev*. 2012; 25(2): 362-386

HOST FACTORS

- Age
  - Strongest predictor of all-cause and infection-related 30-day mortality
- Gender
  - Incidence: males > females
  - Mortality: females > males
- Ethnicity
  - Blacks > whites
- Comorbidities

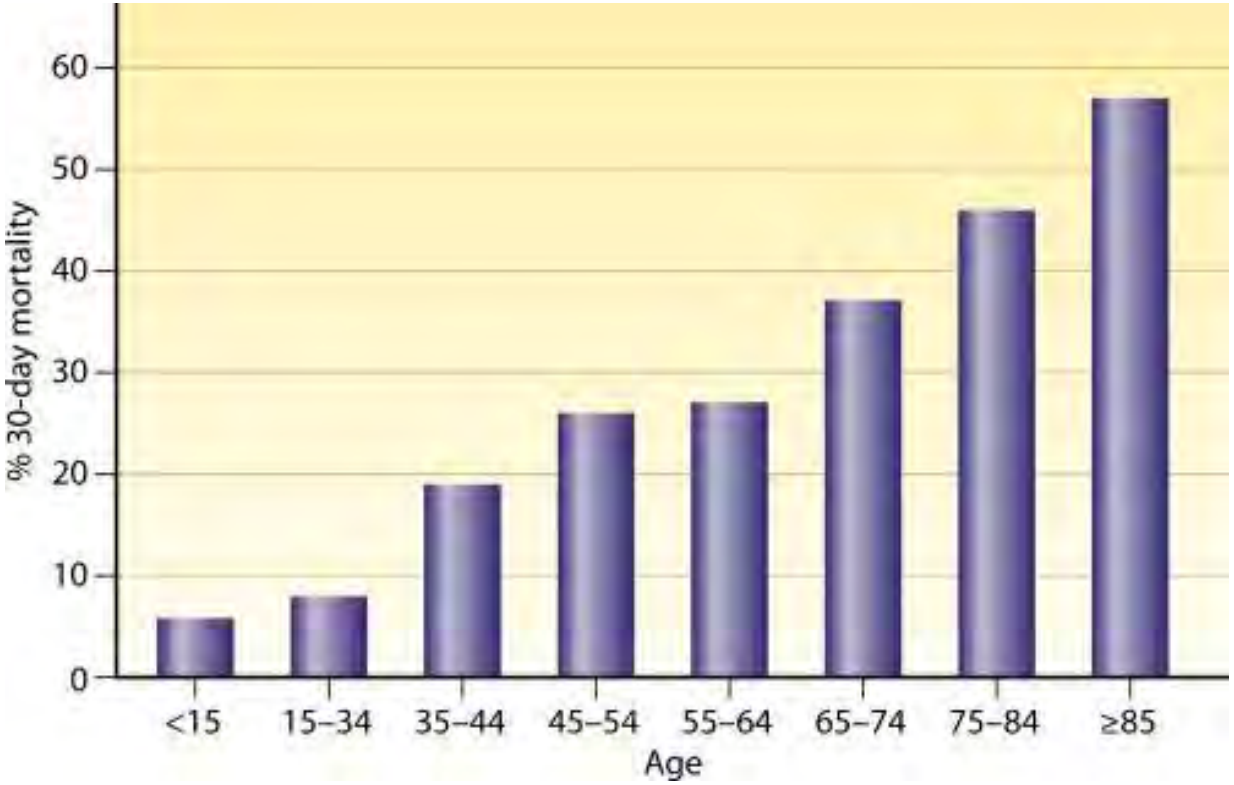

Figure 1. Impact of age on overall 30-day mortality from *Staphylococcus Aureus* bacteremia.

5. *Clin Microbiol Rev*. 2012; 25(2): 362-386

PATHOGEN-HOST INTERACTIONS

- Principle diagnosis and source of infection. Highest mortality rates occur in patients with:
  - Bacteremic pulmonary infections
  - Infective endocarditis (IE)
  - Shock/sepsis
- Mortality rates for SAB secondary to medical device infections
  - Central line – 20.5%
  - Peripheral line – 16.9%
  - Orthopedic implants – 8.3%
  - Hemodialysis catheter – 6.8%

5. *Clin Microbiol Rev*. 2012; 25(2): 362-386

PATHOGEN-HOST INTERACTIONS

- Setting of Bacteremia
  - Two studies observed ⇧ 30-day mortality rates in hospital onset SAB
  - Most cohort studies found SAB setting does not influence outcomes
- Persistent Bacteremia
  - More common in MRSA than MSSA
  - Surrogate for complicated SAB; higher likelihood of metastatic infection
- Bacteriuria
  - Uncommon uropathogen
  - Higher disease burden or complicated SAB?
  - 32% mortality rate compared to 14% without bacteriuria

5. *Clin Microbiol Rev*. 2012; 25(2): 362-386

PATHOGEN SPECIFIC FACTORS

- Methicillin resistance (mecA gene)
  - 1-2x odds of mortality with MRSA bacteremia compared to MSSA bacteremia
- Vancomycin MIC
  - Debatable
  - MIC ≥ 1.5 vs < 1.5
- Exotoxins

	Staphylococcus aureus	
Drug	MIC Interp	MIC Dilutn
Clindamycin	S	<=0.25
Erythromycin	S	<=0.25
Linezolid	S	2
Oxacillin	S	0.5
Penicillin-G	R	>=0.5
Tetracycline	S	<=1
Trimethoprim/Sulfa	S	<=10
Vancomycin	S	<=0.5

	Methicillin-Resistant Staphylococcus aureus	
Drug	MIC Interp	MIC Dilutn
Clindamycin	R	>=8
Erythromycin	R	>=8
Linezolid	S	2
Oxacillin	R	
Penicillin-G	R	>=0.5
Tetracycline	R	>=16
Trimethoprim/Sulfa	S	<=10
Vancomycin	S	1.0

Image source: Cerner Millenium

5. *Clin Microbiol Rev*. 2012; 25(2): 362-386

6. *JAMA*. 2014; 312(15): 1552-64

SAB MANAGEMENT

Patient Case #1a

AH is a 27 year old female presents to the ED with fever, hypotension, and malaise. She has a history of IV drug use and no other medical issues. The sepsis protocol is initiated, two sets of blood cultures are obtained, and she is started on vancomycin and piperacillin-tazobactam.

AH's blood cultures return growing 1 of 2 *Staphylococcus aureus*, mecA positive.

TEST QUESTION #1

Which option provides the most appropriate care for AH?

A. Ignore the blood cultures; it's a contaminant
B. De-escalate the antibiotics to cefazolin and consult infectious diseases
C. Repeat the blood cultures and de-escalate the antibiotics to vancomycin
D. Get an echocardiogram

General Management

- Blood cultures
  - Repeat every 2-4 days after initial positive and as needed to document clearance
- Source identification and control
- Echocardiography
  - Transesophageal echocardiography (TEE) > transthoracic echocardiography (TTE)
- Targeted antibiotic therapy with appropriate duration
- Infectious Diseases consult

7. *CID*. 2011; 52(3): e18-e55

ANTIBIOTIC THERAPY

What about oral antibiotics?

MSSA

- Nafcillin 2g IV every 4 hours
- Oxacillin 2g IV every 4 hours
- Cefazolin 2g IV every 8 hours
  - Caution: cefazolin inoculum effect

MRSA

- Vancomycin IV
  - Goal: AUC 400-600
- Daptomycin 6mg/kg IV
  - Up to 8-10mg/kg/dose

- PLUS rifampin 300mg IV/PO every 8 hours or 600mg PO daily
  - Dependent on source of bacteremia

7. *CID*. 2011; 52(3): e18-e55
8. *Circulation*. 2015; 132: 1435-1486
9. *Am J Health-Syst Pharm*. 2020; 77: 835-864
10. *Microb Drug Resist*. 2014; 20(6): 568-574

BUPHA-INTR ET AL

Design	Retrospective cohort (n = 100 patients)
Intervention	Early oral switch (EOS) prior to 14 days N = 16 in IV group vs N = 84 in EOS group
Inclusion criteria	Health-care associated low risk *Staphylococcus aureus* bacteremia (LR-SAB) ≥18 years
Exclusion criteria	Dialysis dependent during treatment Died or palliated prior to LR-SAB assessment Neutropenia <0.5 x 10^9/L at time of initial blood culture
Outcome	Occurrence of a SAB-related complication within 90 days

27. *Antimicrob Agents Chemother*. 2020; 64(6):e02345-19

BUPHA-INTR ET AL

- IV group more likely to have echo performed
- Flucloxacillin most common IV and oral antibiotic used
- 86% of oral therapy in EOS was with beta-lactams
- 76% of patients switched before 7 days of IV therapy
- 30% penicillin-susceptible *Staphylococcus aureus* (PSSA), 65% MSSA, 5% MRSA bacteremia

27. *Antimicrob Agents Chemother*. 2020; 64(6):e02345-19

Characteristic	No. (%) EOS group ($n = 84$)	i.v. group ($n = 16$)	P
ID consultation	76 (91)	13 (81)	0.28
Negative surveillance BC performed[b]	73 (87)	12 (75)	0.22
Within 72 h of initial positive BC	59 (70)	7 (44)	0.05
Echocardiogram performed	41 (49)	13 (81)	0.03
TTE alone	32 (38)	9 (56)	0.18
TEE alone	6 (7)	2 (13)	0.47
Both TTE and TEE	3 (4)	2 (13)	<0.01
No echocardiography	43 (51)	3 (19)	0.03
i.v. antibiotic therapy			
Flucloxacillin	62 (74)	13 (81)	0.53
Cefazolin	6 (7)	2 (13)	0.47
Vancomycin	5 (6)	1 (6)	0.96
Benzylpenicillin	5 (6)	0 (0)	0.32
Other beta-lactam	4 (5)	0 (0)	0.37
No i.v. antibiotic	2 (2)	0 (0)	0.54
Oral antibiotic therapy			
Flucloxacillin	60 (71)	2 (13)	
Cefalexin	7 (8)	1 (6)	
Other beta-lactam	5 (6)	0 (0)	
Co-trimoxazole	5 (6)	0 (0)	
Clindamycin	3 (4)	0 (0)	
Adjunctive probenecid	5 (6)	0 (0)	
No oral antibiotic	4 (5)[c]	13 (81)	
Median antibiotic therapy duration, days (IQR)			
i.v. therapy	5 (4–6)	14 (14–15)	
Oral therapy	10 (9–14)	6 (2–12)	
Total	16 (14–18)	14 (14–17)	
EOS			
EOS before 7 days of i.v. therapy	64 (76)		
EOS before 10 days of i.v. therapy	82 (98)		
Reasons for no oral switch prior to 14 days			
Clinical decision by ID team not to switch		5 (31)	
EOS advice from ID team not followed		8 (50)	
Compromised oral intake/absorption		3 (19)	

BUPHA-INTR ET AL

Results	SAB recurrence within 90 days occurred in three patients in the EOS group vs one patient in the UV groyo (p = 0.64)
Strengths	One of the only studies that evaluates specifically beta-lactams for SAB
Limitations	Single center, retrospective, observational Small sample size

27. *Antimicrob Agents Chemother*. 2020; 64(6):e02345-19

Oral Antibiotics for SAB

- Potentially useful in uncomplicated SAB
  - However, difficulty in differentiating complicated vs uncomplicated
  - Low incidence of uncomplicated cases in the literature
- Best oral treatment regimen is unknown
  - POET trial: underpowered to draw conclusions in patients with *S. aureus* endocarditis; no patients with MRSA; only 5 patients with injection drug use
  - Jorgensen et al. (2019): no difference in 90-day clinical failure; no subanalysis to evaluate different oral regimens

22. *Open Forum Infect Dis.* 2020; 7(6):ofaa151

CEFAZOLIN INOCULUM EFFECT (CIE)

- *In vitro* studies: increase in the MIC in the presence of a large number of bacteria (endocarditis, osteomyelitis, septic arthritis, etc)
  - High inoculum – 5 x 10^7 CFU/mL or greater
- Observed in specific strains of MSSA
  - Produce type A beta-lactamase (blaZ gene)
- Presence of MSSA strains depends on geographic region
  - USA: 19-27%
  - South America: 26-46%
  - South Korea: 13-58%
  - Japan: 6%

15. *Clin Microbiol Infect.* 2019; 25(7): 818-827

16. https://clsi.org/about/blog/ast-news-update-2019-hot-topic/

CEFAZOLIN VS ANTI-STAPHYLOCOCCAL PENICILLINS

- Systematic review (2019) and narrative review (2018)
  - No randomized controlled trials
  - All cohort studies
  - Cefazolin may be associated with lower 30-day mortality rates (RR 0.70) and less nephrotoxicity (RR 0.36)
    - Equal 30-day and 90-day mortality between therapies for patients with endocarditis or abscesses
- Clinically, CIE does not seem to affect outcomes
  - However, should be aware of possible phenomenon

15. *Clin Microbiol Infect.* 2019; 25(7): 818-827

17. *Clin Microbiol Infect.* 2018; 24(2): 125-132

VANCOMYCIN FOR MSSA BACTEREMIA

- Not recommended
- Associated with higher rates of infection-related mortality, re-infection, and bacteriologic failure compared to cefazolin and anti-staphylococcal penicillins
- Vancomycin likely inferior to beta-lactams in the treatment of MSSA bacteremia

18. *Ann Clin Microbiol Antimicrob*. 2016; 15: 27.

19. *CID*. 2007; 44(2): 190-196.

VANCOMYCIN MIC

- MIC creep phenomenon
  - Single center studies reporting increases in mean vancomycin MIC leading to failure in patients with *S. aureus* infections
  - Newer studies find no evidence of phenomenon
  - Prior MIC creep phenomenon could be due to over-calling and under-calling of MICs between different testing systems
- MIC = 2
  - Some studies suggest increased risk of treatment failure
  - Recent meta-analysis did not support this
  - Regardless of MIC, poor clinical response to vancomycin warrants alternative agent

20. *Clin Microbiol Infect.* 2018; 24(2): 97-104

21. *Infect Chemother*. 2016; 48(4): 267-273

Antibiotic Duration of Therapy

Uncomplicated – 2 weeks

- Negative TTE/TEE
- No implanted prosthesis
- Negative repeat blood cultures
- Defervescence within 72 hours of initiating effective therapy
- No evidence of metastatic sites
- Source control achieved

Complicated – 4-6 weeks

- Not meeting criteria for uncomplicated infection
- Examples:
  - Endocarditis
  - Osteomyelitis/Diskitis
  - Empyema

7. *CID*. 2011; 52(3): e18-e55

11. *CID*. 2015; 61(6): e26-46

INFECTIOUS DISEASES CONSULT

- Associated with better adherence to quality measures and treatment recommendations
  - Repeat blood cultures to clearance
  - Appropriate targeted antibiotic and sufficient duration
  - Echocardiogram
  - Source control
- Reduced in-hospital mortality
- Earlier discharge in patients with SAB
- Improved post-discharge outcomes and reduces risk for new bacteremia episodes

12. *CID*. 2015; 60(10): 1451-1461

13. *JAMA Netw Open*. 2020; 3(2):e1921048

14. *Open Forum Infect Dis.* 2019; 6(12): ofz495

Patient Case #1a

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D. Get an echocardiogram

PATIENT CASE #1B

AH underwent an echocardiogram and a 0.6cm vegetation was found on her tricuspid valve. Unfortunately, she is not qualified for a surgical intervention and she will be managed with antibiotics only.

TEST QUESTION #2

Is AH a candidate for oral antibiotics?

A. Yes, she is an IV drug user and oral antibiotics would be the best option as an outpatient
B. No, she has MRSA bacteremia, complicated by endocarditis
C. Yes, per the results of POET study, she is a good candidate for oral antibiotics
D. No, she has uncomplicated MSSA bacteremia

COMBINATION THERAPY

Proposed Mechanisms of Action

- Increased antibiotic binding
- Reductions in cell wall thickness
- Changes in bacterial membrane charge
- Increased killing by host immune factors
- “See-saw” effect

23. *Pharmacotherapy*. 2020; 40(7):648-658

COMBINATION THERAPY - MSSA

MSSA Combinations

Positive Outcome

- Ulloa et al
  - Cefazolin + ertapenem

Negative/Neutral Outcome

- Grillo et al
  - B-lactam + daptomycin
- Cheng et al
  - Cefazolin/cloxacillin + daptomycin

24. *CID.* 2019; ciz995

25. *CID.* 2019; 69(9): 1480-8

26. *CID.* 2020; ciaa1000

Ulloa Et Al

Design	Retrospective case series (n = 11 cases)
Intervention	Switch to cefazolin + ertapenem
Inclusion criteria	Persistent MSSA bacteremia • Median duration of bacteremia prior to switch was 6 days (range 4-9 days)
Results	All 11 cases were successfully cleared • 6 cases with confirmed endocarditis • Among 9 cases with daily blood cultures, 8 cases cleared within 24h
Limitations	Small sample size Observational, no comparator

24. *CID.* 2019; ciz995

Ulloa Et Al – Cefazolin Inoculum Effect

- Three of 6 MSSA isolates further examined in the study showed a cefazolin inoculum effect
  - One patient experienced overt clinical failure requiring readmission a few days after ertapenem was discontinued and patient was left on cefazolin monotherapy
  - Testing of nafcillin and ertapenem showed no inoculum effect
- Rationale: ertapenem affinity to PBP1 complements cefazolin proclivity to PBP2
  - Ertapenem may serve to “rescue” activity of cefazolin occurring in high inoculum microenvironments

24. *CID.* 2019; ciz995

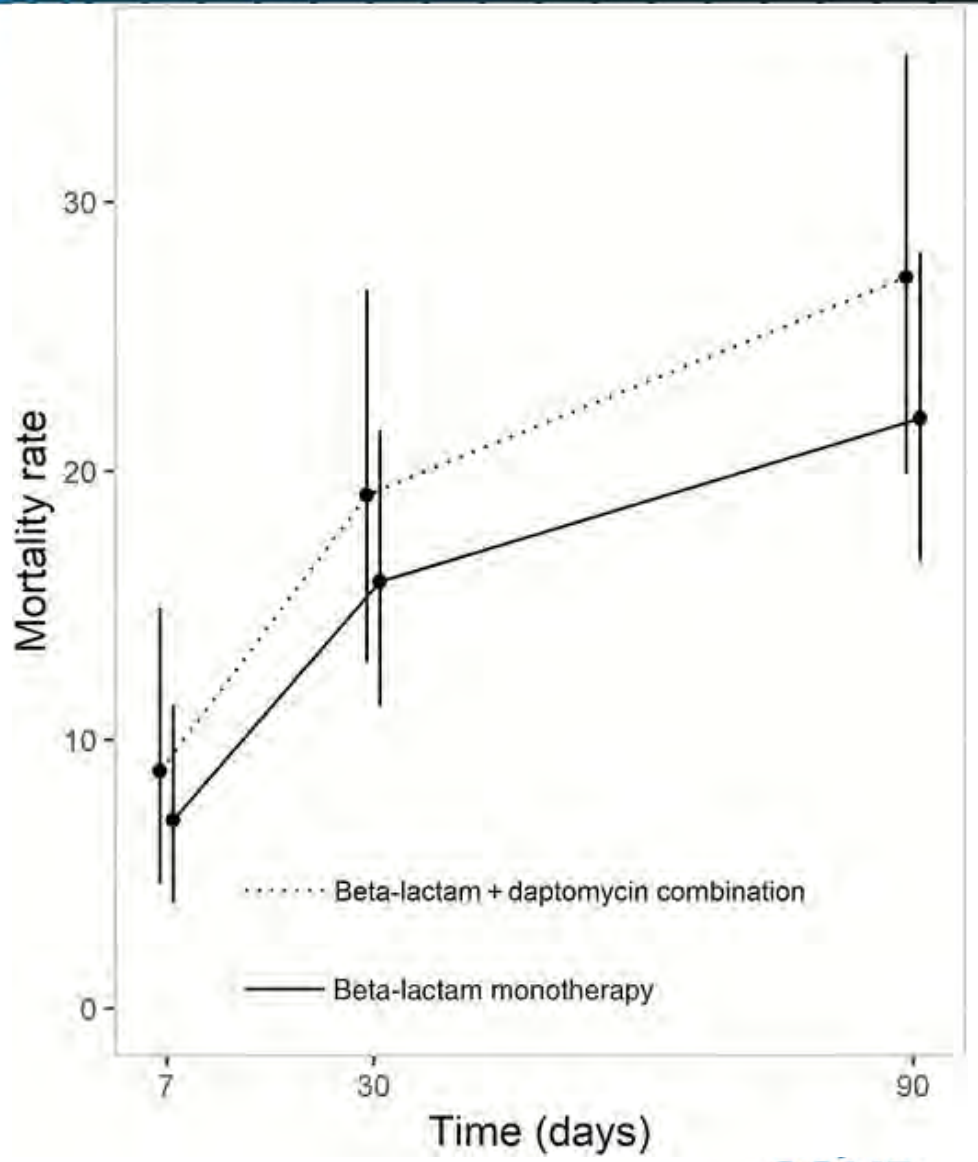
GRILLO ET AL

Design	Retrospective cohort (n = 350 patients)
Intervention	B-lactam monotherapy (BL-M) vs B-lactam in combo with daptomycin (BL/D-C) (10mg/kg)
Inclusion criteria	Adults (≥18 years) MSSA bacteremia
Exclusion criteria	Patients with pneumonia Initiated on BL/D-C > 72 hours after bacteremia onset Antibiotic treatment duration <72 hours Died in the first 48 hours
Outcome	Mortality at 7, 30, and 90 days after the onset of bacteremia

25. *CID.* 2019; 69(9): 1480-8

GRILLO ET AL

Results	All-cause mortality was 7.7%, 17.1%, and 24% at 7, 30, and 90 days, respectively. No differences in mortality rates Propensity score matching: similar mortality rates between groups
Limitations	Retrospective design Greater proportion of severe bacteremia cases occurred in BL/D-C group • Propensity score matching still showed no difference B-lactam therapy undefined



25. *CID.* 2019; 69(9): 1480-8

CHENG ET AL (DASH STUDY)

Design	Randomized, double blind, placebo-controlled (n = 104 patients)
Intervention	Cefazolin/cloxacillin monotherapy vs Addition of 5-day course of daptomycin (6mg/kg) or placebo
Inclusion criteria	Adults (≥18 years) with MSSA bacteremia
Exclusion criteria	Expected to die within 5 days Unable to receive beta-lactam or daptomycin Required additional antibiotics Receiving open label daptomycin
Outcome	Duration of MSSA bacteremia

26. *CID.* 2020; ciaa1000

Cheng Et Al

Results	Primary: Median duration of bacteremia 2.04 days in daptomycin groups vs 1.65 days in monotherapy group (p=0.40) mITT population – 3.1 days in dapto group vs 3 days in mono group Secondary: 90-day mortality – 17.7% mono arm vs 18.9% in dapto arm
Strengths	Randomized, placebo-controlled, double-blinded
Limitations	Significant portion of patients were no longer bacteremic at time of randomization and treatment initiation Randomization occurred within 72 hours of index blood culture Most patients received antibiotics prior to enrollment Small sample size

 26. *CID.* 2020; ciaa1000

MSSA Combination Conclusions

- More robust studies needed
- What combinations of antibiotics have synergistic effects?
  - Daptomycin plus B-lactams – probably ineffective
  - Cefazolin plus ertapenem – more trials needed
- Best population?
  - From onset of bacteremia?
  - Salvage therapy?

COMBINATION THERAPY - MRSA

MRSA Combinations – Positive Outcome

Combination as Initial Therapy

- Davis et al 2016 – RCT
- Casapao et al 2017 – cohort
- Truong et al 2018 – cohort
- McCreary et al 2019 – cohort
- Geriak et al 2019 – RCT
- Zasowski et al 2019 – cohort
- Jorgensen et al OFID 2019 – cohort
- Jorgensen et al CID 2019 – cohort
- Alosaimy et al 2020 – cohort
- Kale-Pradhan et al 2020 – meta-analysis

Combination After Treatment Failure

- Hornak et al 2019 – cohort
- Cortes-Penfield et al 2019 – cohort

Study	Antibiotic Combination Studied
Combination As Initial Therapy	
Davis et al 2016	Vancomycin + flucloxacillin
Casapao et al 2017	Vancomycin + B-lactam (most common piperacillin-tazobactam [54.4%])
Truong et al 2018	Vancomycin + B-lactam (most common piperacillin-tazobactam [54%])
McCreary et al 2019	Daptomycin + ceftaroline
Geriak et al 2019	Daptomycin/vancomycin + ceftaroline
Zasowski et al 2019	Vancomycin + cefepime
Jorgensen et al OFID 2019	Vancomycin + cefazolin
Jorgensen et al CID 2019	Daptomycin + B-lactam (most common cefepime [43.1%], then cefazolin [25%], ceftaroline [9.7%], and ceftriaxone [9.7%])
Alosaimy et al 2020	Daptomycin/vancomycin + B-lactam (most common cefepime [45.9%], then cefazolin [33.6%] and ceftaroline [12.2%])
Combination After Treatment Failure	
Hornak et al 2019	Daptomycin/vancomycin + ceftaroline
Cortes-Penfield et al 2019	Daptomycin + ceftaroline

MRSA Combinations – Negative/Neutral Outcome

Combination as Initial Therapy

- Tong et al 2020 – RCT

Combination After Treatment Failure

- Ahmad et al 2020 – cohort

Study	Antibiotic Combination Studied
Combination As Initial Therapy	
Tong et al 2020	Vancomycin/daptomycin + flucloxacillin/cloxacillin(65.3%)/cefazolin(34.7%)
Combination After Treatment Failure	
Ahmad et al 2020	Daptomycin + ceftaroline

Tong Et Al (CAMERA2 Study)

JAMA Network

QUESTION In adults with methicillin-resistant *Staphylococcus aureus* (MRSA) bacteremia, does the addition of 7 days of an antistaphylococcal β-lactam to standard antibiotic therapy (vancomycin or daptomycin) lead to improved clinical outcomes at 90 days?

CONCLUSION This randomized trial found that the addition of an antistaphylococcal β-lactam to standard antibiotic therapy did not significantly reduce the primary composite end point in patients with MRSA bacteremia.

POPULATION

231 Men
121 Women

Adults hospitalized with MRSA bacteremia

Mean age: 62 years

INTERVENTION

345 Patients analyzed

170 **Combination therapy**
IV vancomycin or daptomycin for 14-42 days plus IV β-lactam for 7 days

175 **Standard therapy**
IV vancomycin or daptomycin for 14-42 days

LOCATIONS

27
Hospitals in Australia, Singapore, New Zealand, and Israel

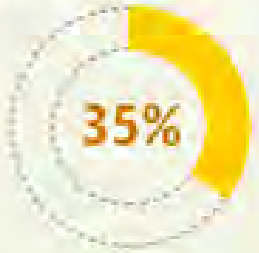
PRIMARY OUTCOME

Composite at 90 days of all-cause mortality, persistent bacteremia at day 5, microbiological relapse, and microbiological failure

FINDINGS

All-cause mortality, persistent bacteremia at day 5, microbiological relapse, and microbiological failure

Combination therapy
59 of 170 patients



Standard therapy
68 of 175 patients

The primary outcome was not significant:

Between-group difference: −4.2%
(95% CI, −14.3% to 6.0%)

Tong SYC, Lye DC, Yahav D, et al. 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 [published February 11, 2020]. *JAMA*. doi:10.1001/jama.2020.0103

TONG ET AL (CAMERA2 STUDY)

- The trial was stopped early
  - Significant acute kidney injury (AKI) in the combination therapy group
    - 23% in combination therapy vs 6% in standard therapy ($p<0.001$)
    - Majority of combination therapy patients received a combinations of flucloxacillin and vancomycin
      - Suspected that flucloxacillin may be culprit for high incidence of AKI

28. *JAMA*. 2020; 323(6):527-537.

KALE-PRADHAN ET AL

Design	Meta-analysis (n = 9 studies, 1636 patients)
Objective	Compare clinical failure with combination vancomycin/daptomycin with a B-lactam vs vancomycin/daptomycin monotherapy
Inclusion criteria	Studies evaluating clinical outcomes associated with the addition of a B-lactam antibiotic to standard vancomycin, daptomycin or teicoplanin montherapy in patients with confirmed MRSA bacteremia or infected endocarditis
Exclusion criteria	In-vitro data Animal model studies Case reports/case series Combination therapy started only after clinical failure

23. *Pharmacotherapy*. 2020; 40(7): 648-658

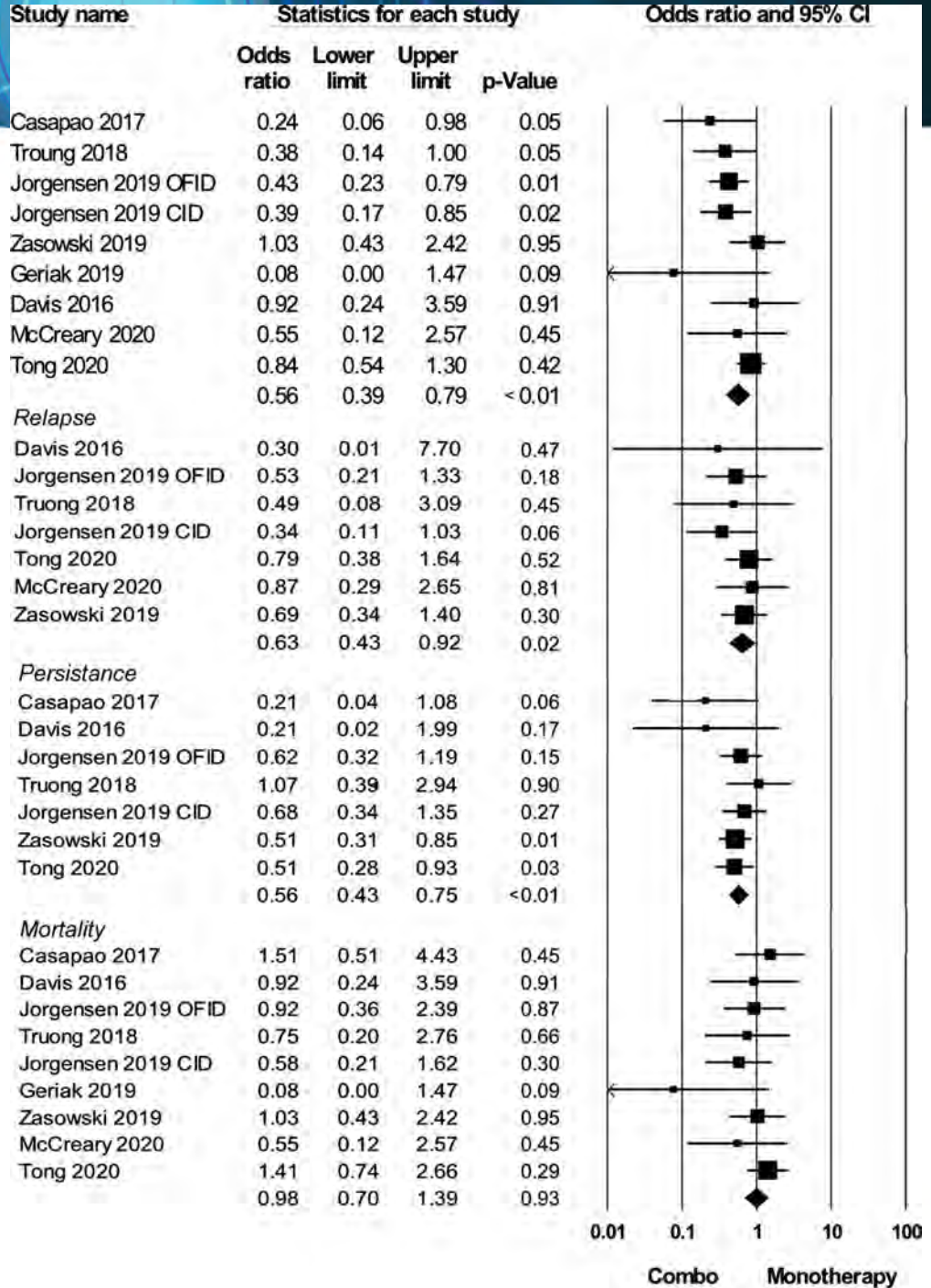
Lower clinical failure rates with combination therapy vs monotherapy (p <0.01)

Lower rates of bacteremia relapse (p = 0.01) and persistent bacteremia

(p = 0.01) with combination therapy vs monotherapy

No significant differents in mortality between groups

(p = 0.93)



Study name	Odds ratio	Lower limit	Upper limit	p-Value
Casapao 2017	0.24	0.06	0.98	0.05
Troung 2018	0.38	0.14	1.00	0.05
Jorgensen 2019 OFID	0.43	0.23	0.79	0.01
Jorgensen 2019 CID	0.39	0.17	0.85	0.02
Zasowski 2019	1.03	0.43	2.42	0.95
Geriak 2019	0.08	0.00	1.47	0.09
Davis 2016	0.92	0.24	3.59	0.91
McCreary 2020	0.55	0.12	2.57	0.45
Tong 2020	0.84	0.54	1.30	0.42
	0.56	0.39	0.79	<0.01
Relapse				
Davis 2016	0.30	0.01	7.70	0.47
Jorgensen 2019 OFID	0.53	0.21	1.33	0.18
Truong 2018	0.49	0.08	3.09	0.45
Jorgensen 2019 CID	0.34	0.11	1.03	0.06
Tong 2020	0.79	0.38	1.64	0.52
McCreary 2020	0.87	0.29	2.65	0.81
Zasowski 2019	0.69	0.34	1.40	0.30
	0.63	0.43	0.92	0.02
Persistance				
Casapao 2017	0.21	0.04	1.08	0.06
Davis 2016	0.21	0.02	1.99	0.17
Jorgensen 2019 OFID	0.62	0.32	1.19	0.15
Truong 2018	1.07	0.39	2.94	0.90
Jorgensen 2019 CID	0.68	0.34	1.35	0.27
Zasowski 2019	0.51	0.31	0.85	0.01
Tong 2020	0.51	0.28	0.93	0.03
	0.56	0.43	0.75	<0.01
Mortality				
Casapao 2017	1.51	0.51	4.43	0.45
Davis 2016	0.92	0.24	3.59	0.91
Jorgensen 2019 OFID	0.92	0.36	2.39	0.87
Truong 2018	0.75	0.20	2.76	0.66
Jorgensen 2019 CID	0.58	0.21	1.62	0.30
Geriak 2019	0.08	0.00	1.47	0.09
Zasowski 2019	1.03	0.43	2.42	0.95
McCreary 2020	0.55	0.12	2.57	0.45
Tong 2020	1.41	0.74	2.66	0.29
	0.98	0.70	1.39	0.93

23. *Pharmacotherapy*. 2020; 40(7): 648-658

Kale-Pradhan Et Al

- Other outcomes: no difference in nephrotoxicity between the two treatment groups (p=0.18)
- Conclusions
  - Combination therapy associated with lower clinical failure rates → lower rates of relapse and bacteremia persistence
  - No difference seen in mortality
  - Potential use → patients with recurrent MRSA bacteremia?
    - Monotherapy likely sufficient for majority of patients

23. *Pharmacotherapy*. 2020; 40(7): 648-658

TEST QUESTION #3

Which type of patient and antibiotic combination would likely have the best clinical outcome?

A. Patient with uncomplicated MSSA bacteremia on cefazolin and ertapenem
B. Patient with persistent MSSA bacteremia on cefazolin and daptomycin
C. Patient with complicated MRSA bacteremia on vancomycin and flucloxacillin
D. Patient with recurrent MRSA bacteremia on daptomycin and ceftaroline

CONCLUSIONS

MRSA/MSSA BACTEREMIA

- High morbidity and mortality
- Important to ensure care bundle is initiated
  - Repeat blood cultures until negative
  - Source control
  - Echocardiogram
  - Appropriate antibiotics
    - When to use oral?
    - When to use combination? What combination is best?
- Infectious Diseases consult

Patient Case #1a

AH is a 27 year old female presents to the ED with fever, hypotension, and malaise. She has a history of IV drug use and no other medical issues. The sepsis protocol is initiated, two sets of blood cultures are obtained, and she is started on vancomycin and piperacillin-tazobactam.

AH's blood cultures return growing 1 of 2 *Staphylococcus aureus*, mecA positive.

TEST QUESTION #1

Which option provides the most appropriate care for AH?

A. Ignore the blood cultures; it's a contaminant
B. De-escalate the antibiotics to cefazolin and consult infectious diseases
C. Repeat the blood cultures and de-escalate the antibiotics to vancomycin
D. Get an echocardiogram

PATIENT CASE #1B

AH underwent an echocardiogram and a 0.6cm vegetation was found on her tricuspid valve. Unfortunately, she is not qualified for a surgical intervention and she will be managed with antibiotics only.

TEST QUESTION #2

Is AH a candidate for oral antibiotics?

A. Yes, she is an IV drug user and oral antibiotics would be the best option as an outpatient
B. No, she has MRSA bacteremia, complicated by endocarditis
C. Yes, per the results of POET study, she is a good candidate for oral antibiotics
D. No, she has uncomplicated MSSA bacteremia

TEST QUESTION #3

Which type of patient and antibiotic combination would likely have the best clinical outcome?

A. Patient with uncomplicated MSSA bacteremia on cefazolin and ertapenem
B. Patient with persistent MSSA bacteremia on cefazolin and daptomycin
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D. Patient with recurrent MRSA bacteremia on daptomycin and ceftaroline

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