Staphylococcus aureus: come gestire al meglio i primi 7 giorni

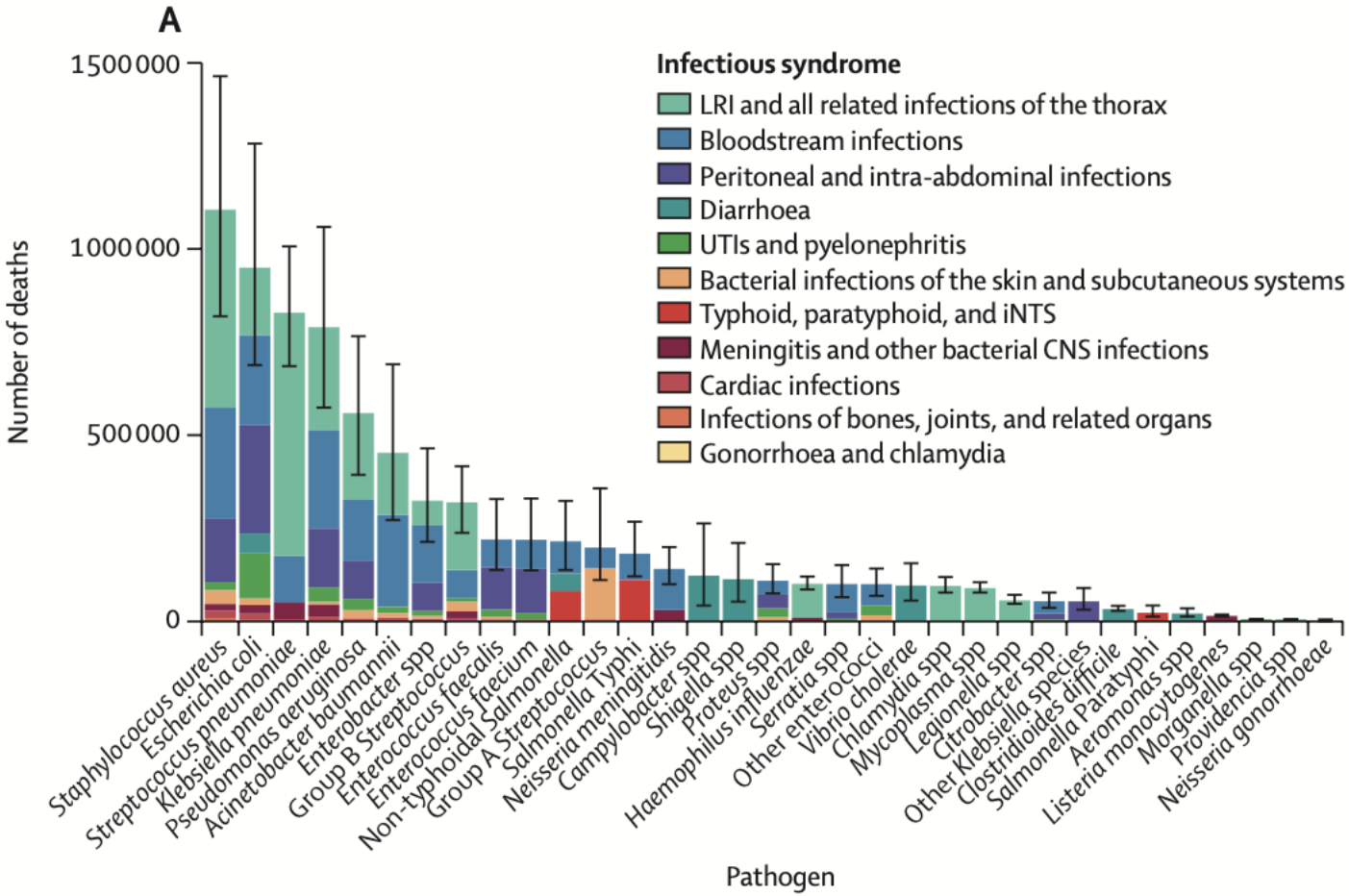
Dott.ssa Stefania Piconi
Direttore S.C. Malattie Infettive
A. Manzoni, ASST Lecco

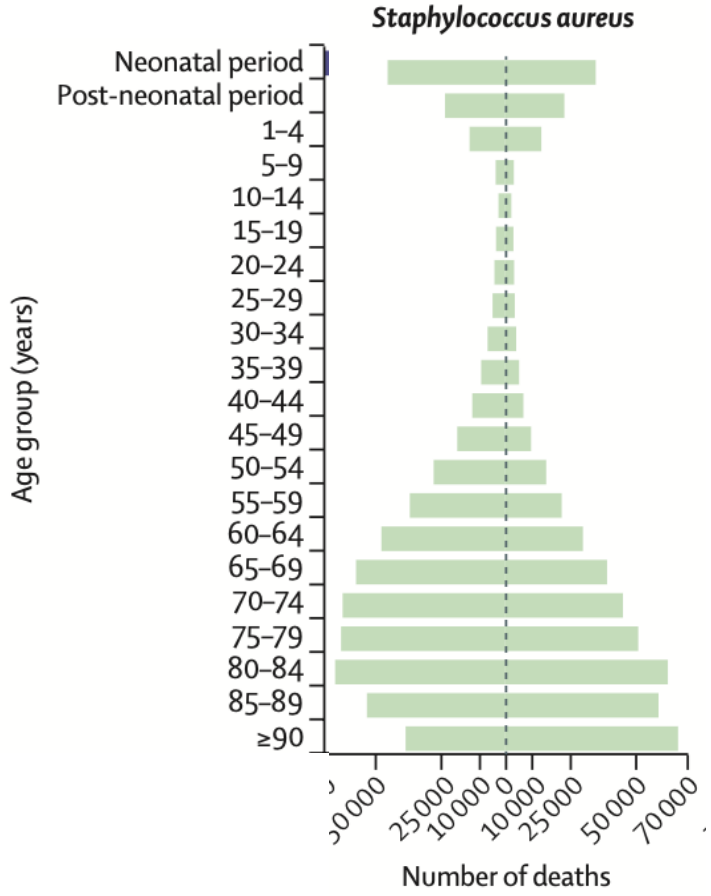
Agenda

- Epidemiology and lethality
- Clinical Characteristics: High Risk and Low Risk
- Persistent *Staphilococcus aureus* Bacteriemia: Definition and Prognosis
- TTE, TEE and 18F-FDG PET/CT Scan: when and for which patients
- Antimicrobial Treatment: Guidelines/RCT and real world data
- Early oral switch of antimicrobial therapy
- Special patients: old patients
- Take-home messages

Lancet 2022;400:2221-48

MRSA and mortality





S aureus was the leading bacterial cause of death in 135 countries and was also associated with the most deaths in individuals older than 15 years, globally.

MRSA BSI causes >300.000 deaths/year worldwide

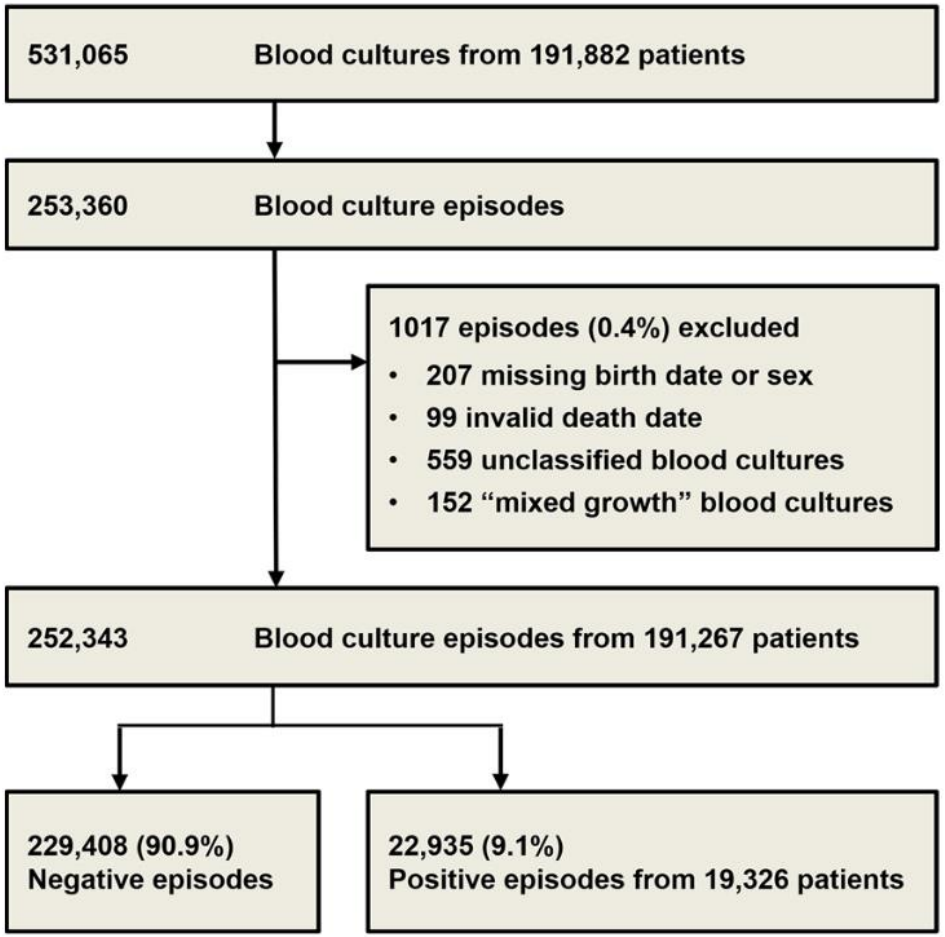
Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study

Mark Verway,[a] Kevin A. Brown,[a,b,c,d] Alex Marchand-Austin,[b,d] Christina Diong,[d] Samantha Lee,[d] Bradley Langford,[b] Kevin L. Schwartz,[b,c,d,e] Derek R. MacFadden,[f] Samir N. Patel,[a,b] Beate Sander,[a,b,d,g] Jennie Johnstone,[a,c] Gary Garber,[a,b,f] Nick Daneman[a,b,d,h]

Aim:
describe the the prevalence of BSIs and examine the associated mortality risk for the responsible microorganisms.

Methods:
retrospective cohort study of BSIs in 2017. Blood culture data was collected from almost all microbiology laboratories in Ontario and linked to data sets of patient characteristics.

Results:
From 531,065 blood cultures, we identified 22,935 positive BSI episodes in 19,326 pts (incidence of 150 per 100,000 population)



Verway M. Journal of Clinical Microbiology 2022;60: 1-10

Prevalence and Mortality Associated with Bloodstream Organisms: a Population-Wide Retrospective Cohort Study

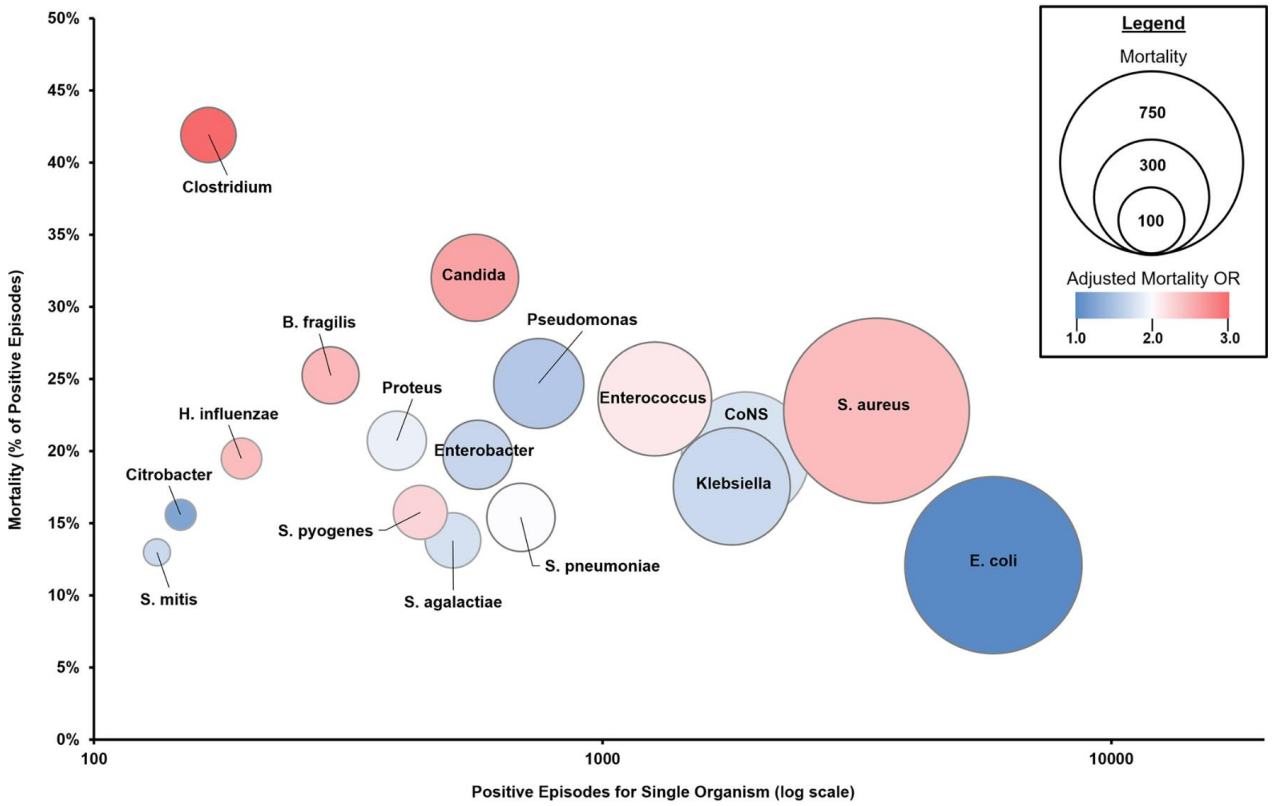
Mortality rate for positive culture episodes 17,0%
Mortality rate for negative culture episode was 9.5%

Mark Verway,[a] Kevin A. Brown,[a,b,c,d] Alex Marchand-Austin,[b,d] Christina Diong,[d] Samantha Lee,[d] Bradley Langford,[b] Kevin L. Schwartz,[b,c,d,e] Derek R. MacFadden,[f] Samir N. Patel,[a,b] Beate Sander,[a,b,d,g] Jennie Johnstone,[a,c] Gary Garber,[a,b,f] Nick Daneman[a,b,d,h]

Results:
Escherichia coli 40.2 per 100,000 population
Staphylococcus aureus 22.4 per 100,000 population
COnS 12.1 per 100,000 population
Klebsiella species 11.1 per 100,000 population
Enterococcus species 7.1 per 100,000 population

The adjusted risk for mortality at 30 days for BSI episodes was
OR 1.47 (95% (CI), 1.41 to 1.54) compared to patients with BC negative
OR 2.62 (95% CI, 2.52 to 2.73) compared to matched patients without blood culture test

Clostridium species were associated with the highest adjusted odds of mortality compared to that of negative cultures (adjusted OR, 5.81; 95% CI, 4.00 to 8.44).
Among high incidence pathogens, Staphylococcus aureus had the highest odds ratio of mortality (adjusted odds ratio, 2.14; 95% CI, 1.94 to 2.36).



Staphylococcus aureus is a prominent threat to public health

Verway M. Journal of Clinical Microbiology 2022;60: 1-10

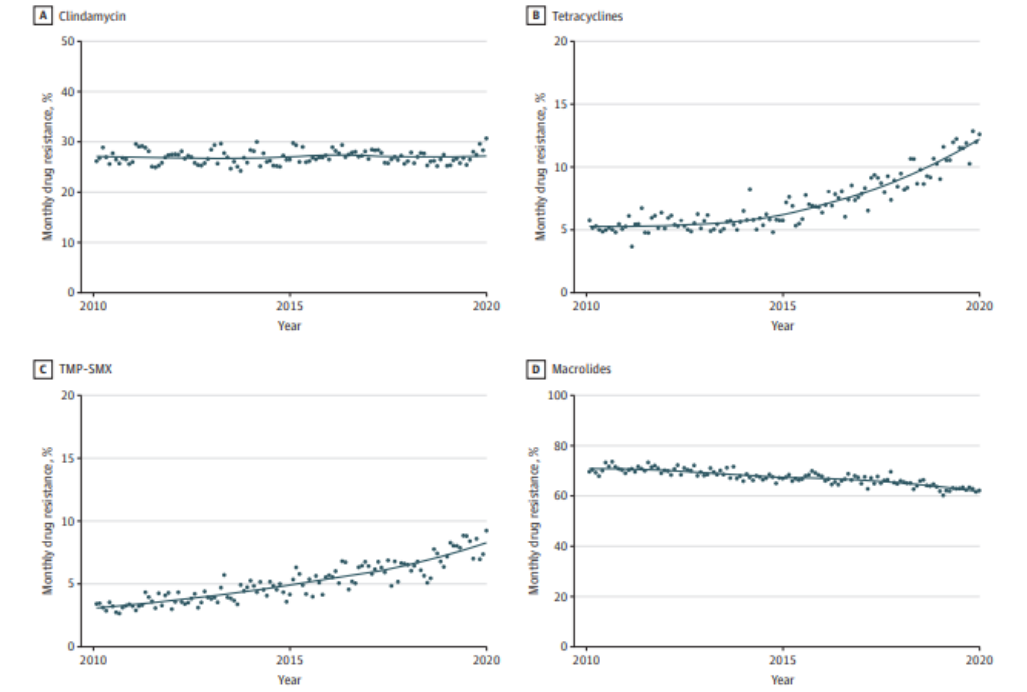
Original Investigation | Infectious Diseases

Antimicrobial Resistance Patterns of Outpatient *Staphylococcus aureus* Isolates

Margaret Carrel, PhD; Matthew Smith, MD, MPH; Qianyi Shi, PhD; Shinya Hasegawa, MD; Gosia S. Clore, MS, MPH; Eli N. Perencevich, MD, MS; Michihiko Goto, MD, MSCI

252910 pts males (94.3%)
mean (SD) age 63.4 (14.8)
S aureus specimens decreased 42003 (2010) to 34437 (2019) monthly variation
MRSA 173 118 (45.3%)

JAMA Network Open. 2024;7(6):e2417199. doi:10.1001/jamanetworkopen.2024.17199 June 14, 2024 4/11



MRSA became less common over the 10-year period, and MRSA isolates were increasingly resistant to tetracyclines and TMP-SMX. Examining the regional variation of antibiotic resistance can inform empirical therapy recommendations and help to understand the evolution of S aureus antibiotic resistance mechanisms

JAMA Network Open. 2024;7(6):e2417199.doi:10.1001/jamanetworkopen.2024.17199

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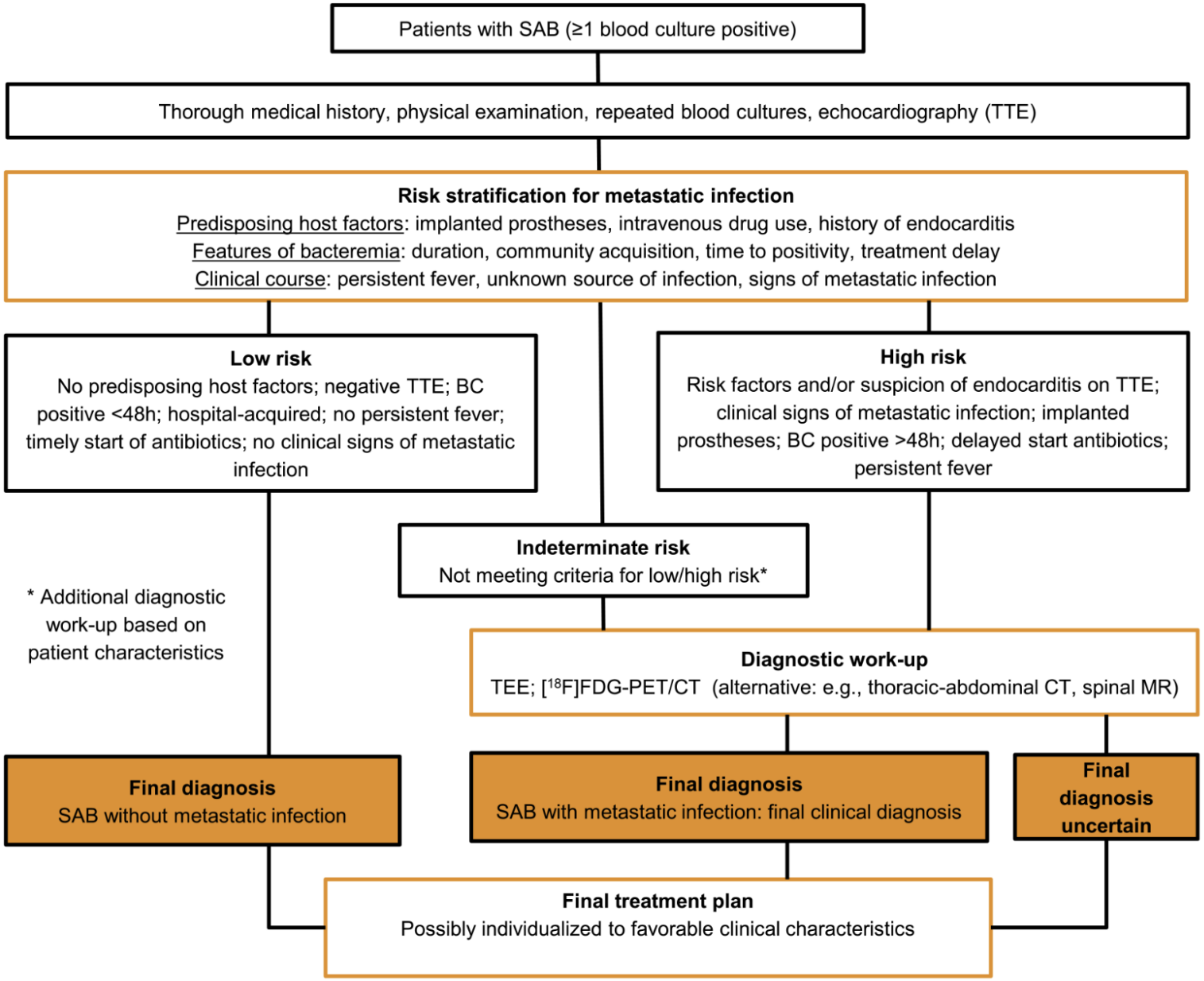
Risk factors for *Staphilococcus aureus* bacteremia

- Central venous catheters
- Implanted cardiac or other prosthetic devices
- Injection drug use
- Hemodialysis
- Recent surgical procedures
- Host factors (age, sex, lower socio economic status, diabetes, corticosteroid use, HIV infection and S aureus nasal colonization)

Soul M. CID 2019;69:1868-1877
Rha B.MMWR 2023; 72:153-159
Laupland KB. Clin Microbiol Infect: 2013;19:456-471
Tong SY. BMC infect Dis. 2012;12:249
Smit J. Eur J Endocrinol 2016;174:631-639
Wertheim HF. Lancet 2004:364:703-705



Redefining *Staphylococcus aureus* bacteremia: A structured approach guiding diagnostic and therapeutic management

Ilse J.E. Kouijzer[a], **Vance G. Fowler Jr.**[b,c], **Jaap ten Oever**[a,*]

[a]Department of Internal Medicine and Radboud Center for Infectious Diseases, Radboudumc, Nijmegen, the Netherlands

[b]Department of Medicine, Duke University, Durham North Carolina, USA

[c]Duke Clinical Research Institute, Durham, North Carolina, USA

Uncomplicated SAB definition (IDSA):

1)EI excluded
2)No implanted prostheses
3)Negative blood cultures 2 to 4 days after initial blood culture
4)Defervescence within 72H of effective therapy
5)No metastatic sites of infection

Kouijzer IJE J Infect 2023; 86: 9–13. doi:10.1016/j.jinf.2022.10.042.

SAB: diagnostic work-up

Goto M. JAMA Internal Medicine 2017; 177:1489-1497

JAMA Internal Medicine | Original Investigation

Association of Evidence-Based Care Processes With Mortality in *Staphylococcus aureus* Bacteremia at Veterans Health Administration Hospitals, 2003-2014

Michihiko Goto, MD, MSCI; Marin L. Schweizer, PhD; Mary S. Vaughan-Sarrazin, PhD; Eli N. Perencevich, MD, MS; Daniel J. Livorsi, MD, MS; Daniel J. Diekema, MD, MS; Kelly K. Richardson, PhD; Brice F. Beck, MA; Bruce Alexander, PharmD; Michael E. Ohl, MD, MSPH

Aim: To examine the association of evidence-based care processes (**use of appropriate antibiotic therapy, echocardiography, and ID consultation**) in routine care for SAB with mortality

Method: retrospective observational cohort study.

Pts with SAB from 2003 to 2014

Results:

36.868 patients in 124 hospitals

Outcomes	RR (95% CI)
30 day mortality	0.58 (0.55-0.60)
90 day mortality	0.70 (0.67-0.72)
Recurrence of bacteremia or 90 day mortality	0.68 (0.66-0.70)

Figure 1. Trends in the Incidence of *Staphylococcus aureus* Bacteremia and All-Cause 30-Day Mortality, 2003-2014

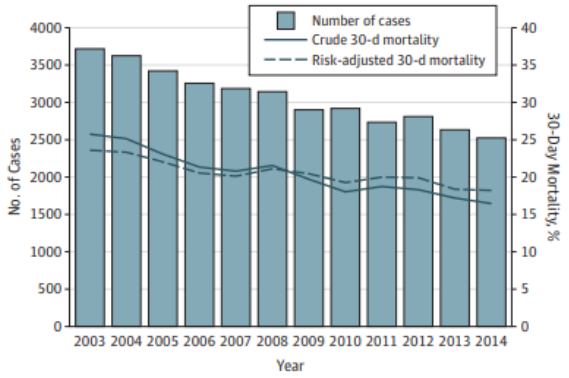


Figure 2. Trends in Rates of Use of Evidence-Based Care Process, 2003-2014

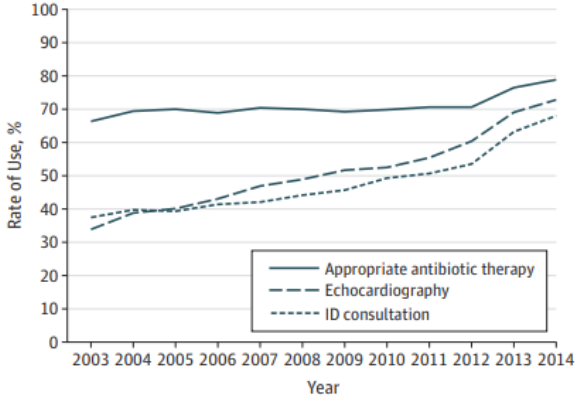
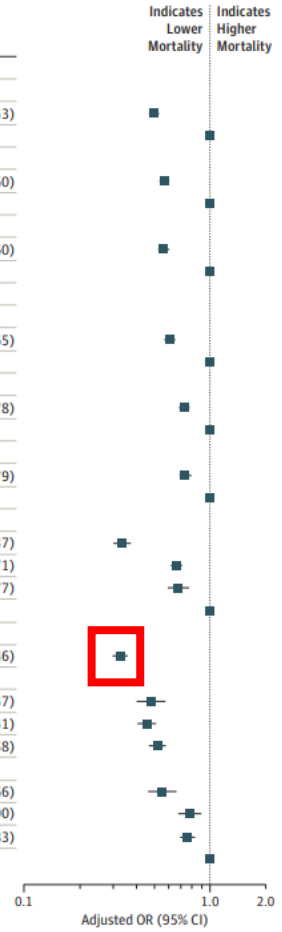


Figure 3. Associations Between Receipt of Evidence-Based Care Processes and 30-Day Mortality

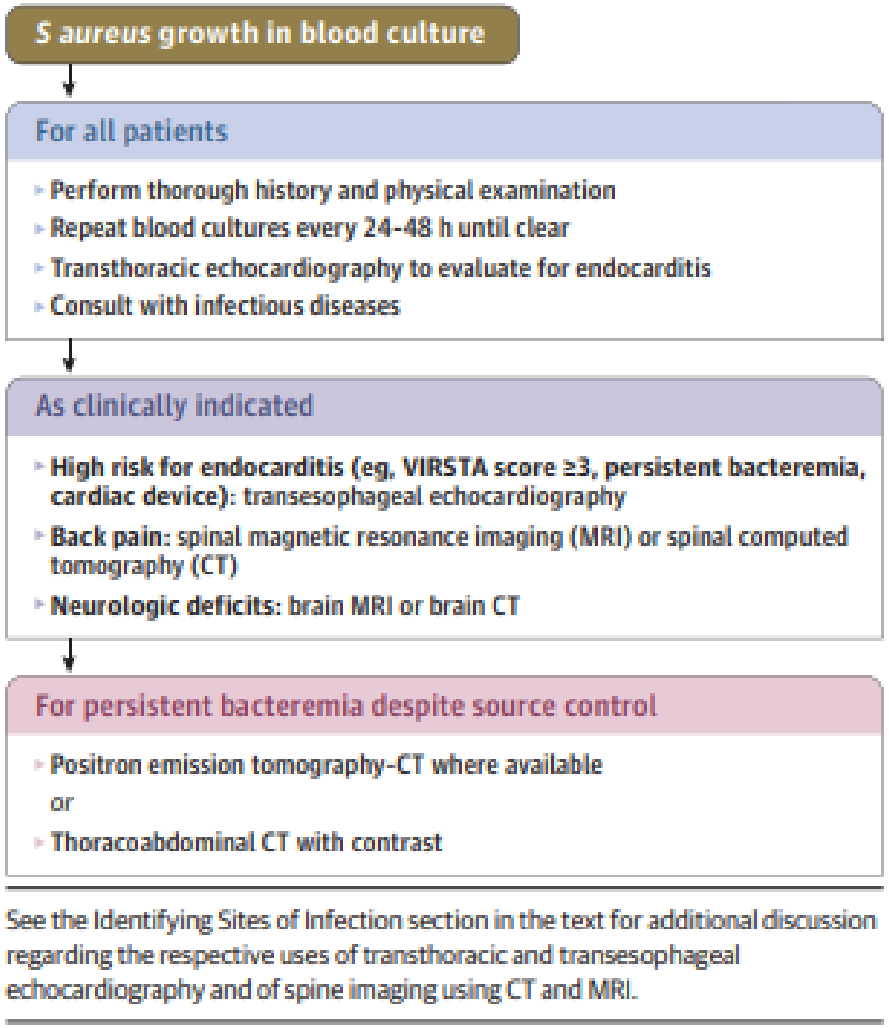
Evidence-Based Care Processes	No. of Patients (%)	Adjusted OR (95% CI)
Process measures (not adjusted for other care processes)		
ID consultation during hospitalization		
ID consultation	17 289 (46.9)	0.50 (0.47-0.53)
No ID consultation	19 579 (53.1)	1 [Reference]
Echocardiography during hospitalization		
Echocardiography	18 345 (49.8)	0.57 (0.53-0.60)
No echocardiography	18 523 (50.2)	1 [Reference]
Appropriate therapy during hospitalization		
Appropriate therapy	26 037 (70.6)	0.56 (0.52-0.60)
Other therapy	10 831 (29.4)	1 [Reference]
Process measures (adjusted for other care processes)		
ID consultation during hospitalization		
ID consultation	17 289 (46.9)	0.61 (0.56-0.65)
No ID consultation	19 579 (53.1)	1 [Reference]
Echocardiography during hospitalization		
Echocardiography	18 345 (49.8)	0.73 (0.68-0.78)
No echocardiography	18 523 (50.2)	1 [Reference]
Appropriate therapy during hospitalization		
Appropriate therapy	26 037 (70.6)	0.74 (0.68-0.79)
Other therapy	10 831 (29.4)	1 [Reference]
Types of echocardiography		
TEE	5522 (15.0)	0.33 (0.30-0.37)
TTE	10 769 (29.2)	0.66 (0.61-0.71)
Undocumented type	2054 (5.6)	0.67 (0.59-0.77)
No echocardiography	18 523 (50.2)	1 [Reference]
Combination of care processes		
All 3 care processes	10 608 (28.8)	0.33 (0.30-0.36)
Two of 3 care processes		
ID consultation and echocardiography	1382 (3.7)	0.48 (0.40-0.57)
ID consultation and appropriate therapy	4012 (10.9)	0.45 (0.40-0.51)
Echocardiography and appropriate therapy	4692 (12.7)	0.52 (0.47-0.58)
One of 3 care processes		
ID consultation only	1258 (3.4)	0.55 (0.46-0.66)
Echocardiography only	1663 (4.5)	0.78 (0.67-0.90)
Appropriate therapy only	6725 (18.2)	0.76 (0.69-0.83)
No care process	6528 (17.7)	1 [Reference]



57.3% (95% CI, 48.4%-69.9%) of the decrease in risk-adjusted mortality between 2003 and 2014 could be attributed to increased use of the 3 evidence-based care processes

SAB: diagnostic work-up

Figure 2. Diagnostic Evaluation of Patients With *Staphylococcus aureus* Bacteremia



See the Identifying Sites of Infection section in the text for additional discussion regarding the respective uses of transthoracic and transesophageal echocardiography and of spine imaging using CT and MRI.

Rapid molecular determination of methicillin resistance in staphylococcal bacteraemia improves early targeted antibiotic prescribing: a randomized clinical trial

S. Emonet [1, 2, *], P.G. Charles [3], S. Harbarth [1], A.J. Stewardson [3], G. Renzi [2], I. Uckay [1], A. Cherkaoui [2], M. Rougemont [1], J. Schrenzel [1, 2, 4]

Table 3
Primary and secondary outcomes for the two groups

Endpoints	Intervention	Control	*p*-Value
Hours from Gram stain to targeted treatment, median (IQR)			
All staphylococci	6.0 (3.8-10.0)	8.0 (1.0–36.0)	0.13
Staphylococcus aureus only	5.0 (3.0-7.0)	25.5 (3.8–54.0)	<0.001
On targeted therapy when standard susceptibility testing complete			
All patients	41/48 (85.4%)	23/41 (56.1%)	0.004
Sub-group with methicillin-susceptible isolates	28/32 (87.5%)	7/22 (31.8%)	<0.001
Sub-group with methicillin-resistant isolates	13/16 (81.3%)	15/19 (78.9%)	1
Hours from Gram stain to transmission of methicillin-susceptibility results, median (IQR)	3.9 (2.8–4.3)	25.4 (24.4–26.7)	<0.001
Need for ICU care	12/48 (25.0%)	11/41 (26.8%)	1
Number of patients with septic complications	18/48 (37.5%)	15/41 (36.6%)	1
Crude 28-day mortality	6/48 (12.5%)	9/41 (22.0%)	0.27
Infection related 28-day mortality	3/48 (6.3%)	6/41 (14.6%)	0.29

Rapid determination of methicillin resistance in staphylococcal bacteraemia is accurate and reduces significantly the time to targeted antibiotic therapy in the subgroup of S. aureus, thereby avoiding unnecessary exposure to vancomycin. There was no significant effect on clinical outcomes

Tong S.Y.C. JAMA. doi:10.1001/jama.2025.4288
Emonet S. Clinical Microbiology and Infection 22 (2016) 946.e9e946.e15

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S. aureus Persistent Bacteriemia (SABP)

- S. aureus is the most common cause of persistent bacteriemia
- SABP occurs in 8-39% of cases of S. aureus bacteriemia
- SABP has been associated with:
  - Increased risk of mortality
  - Increased risk of metastatic spread
  - Increased risk of relapse rate
  - Increased risk of resistance (?)

……*but the SAPB cutoff duration is poorly defined….*

2, 3, 4, 5…or 7 days or even longer?

Welsh KJ. J Clin Microbiol 2011; 49: 3669–72.
Gasch O. Clin Microbiol Infect 2014; 20: 361–67.
Park KH. PLoS One 2012; 7: e46389.
Rose WE. J Infect Dis 2012; 206: 1604–11.
Neuner EA. Diagn Microbiol Infect Dis 2010; 67: 228–33.
Minejima E.Crit Care Med 2016; 44: 671–79.
Guimaraes AO. Clin Infect Dis 2019; 68: 1502–11.

The IDSA recommends re-evaluation of treatment when meticillin-resistant S aureus (MRSA) bacteraemia persists for 7 days despite active antibiotic therapy

Wiggers JB BMC Infect Dis 2016; 16: 286.
Hawkins C Arch Intern Med 2007; 167: 1861–67.
Khatib R. Scand J Infect Dis 2006; 38: 7–14.
Khatib R. Scand J Infect Dis 2009; 41: 4–9.
Chong YP. Medicine 2013; 92: 98–108.
Fowler VG. Arch Intern Med 2003; 163: 2066–72
Fowler VG Jr. J Infect Dis 2004;190: 1140–49

S. aureus Persistent Bacteriemia (SABP)

Positive SAB >48 hours are associated with:	References
Relapse and mortality	**4 studies** *Kuehl Lancet ID 2020, Minejima CID 2020, Albertson 2015, Johnson 2003*
Endovascular focus (EI, septic thrombosis, infected intravascular foreign bodies)	**13 studies** *Fowler AIM 2003, Khatib SJID 2006, Kaasch CID 2011, Chong Med 2013, Chang 2003, Palraj 2015, Gow 2015, Tubiana 2016, Finkelstein 2012, Longobardo 2019, Hill 2007, Papadimitriou-Olivgeris 2022, Grippo 2022*
Deep-seated or metastatic foci	**7 studies** *Fowler AIM 2003, Khatib SJID 2006, Kaasch CID 2011, Tubiana JID 2016, Gasch 2014, Perez 2018, Wang 2023*

Defining persistent *Staphylococcus aureus* bacteraemia: secondary analysis of a prospective cohort study

*Richard Kuehl, Laura Morata, Christian Boeing, Isaac Subirana, Harald Seifert, Siegbert Rieg, Winfried V Kern, Hong Bin Kim, Eu Suk Kim, Chun-Hsing Liao, Robert Tilley, Luis Eduardo Lopez-Cortés, Martin J Llewelyn, Vance G Fowler, Guy Thwaites, José Miguel Cisneros, Matt Scarborough, Emmanuel Nsutebu, Mercedes Gurgui Ferrer, José L Pérez, Gavin Barlow, Susan Hopkins, Hugo Guillermo Ternavasio-de la Vega, M Estée Török, Peter Wilson, Achim J Kaasch, Alex Soriano, on behalf of the International Staphylococcus aureus collaboration study group and the ESCMID Study Group for Bloodstream Infections, Endocarditis and Sepsis**

All outcomes were significantly more frequent in patients with delayed clearance of bacteraemia

Aim:
to evaluate mortality according to duration of SAB

Methods:
Prospective cohort (UK, Spain and Germany) >18y with SAB

Primary outcome: 90-day mortality

Secondary outcomes
30-day-mortality, in-hospital mortality, development of a new metastatic focus

Results:
1588 pts (601 excluded)
365 (37%) pts had at least 1 additional day of bacteraemia

	1 day (n=672)	2–4 days (n=218)	5–7 days (n=69)	>7 days (n=28)	Total (n=987)	p value
Outcome						
30-day mortality	84 (13%)	60 (28%)	21 (30%)	9 (32%)	174 (18%)	<0·0001
90-day mortality	148 (22%)	85 (39%)	30 (43%)	10 (36%)	273 (28%)	<0·0001
In-hospital mortality	101 (15%)	72 (33%)	26 (38%)	9 (32%)	208 (21%)	<0·0001
Any new metastatic focus*	39 (6%)	22 (10%)	15 (22%)	3 (11%)	79 (8%)	<0·0001
New metastatic focus >7 days†	22 (3%)	8 (4%)	6 (9%)	3 (11%)	39 (4%)	0·040
Patient management						
Infectious disease specialist consultation	591 (88%)	188 (86%)	60 (87%)	25 (89%)	864 (88%)	0·97
Transthoracic echocardiography	407 (61%; 2%)	122 (56%; 3%)	37 (54%; 1%)	17 (61%; 0%)	583 (60%; 2%)	0·57
Transoesophageal echocardiography	177 (26%; 3%)	75 (34%; 5%)	32 (46%; 1%)	17 (61%; 0%)	301 (31%; 3%)	<0·0001
Intensive care unit treatment	184 (27%; 3%)	78 (36%; 2%)	30 (43%; 0%)	15 (54%; 0%)	307 (32%; 3%)	0·0008
Combination antibiotic therapy	205 (31%)	77 (35%)	31 (45%)	15 (54%)	328 (34%)	0·0059
Focus of any kind removed	224 (33%)	60 (28%)	19 (28%)	6 (21%)	309 (31%)	0·22
Interval until focus removal, days	0 (–1 to 1; 3%)	0 (0 to 2; 0%)	1 (1 to 5; 11%)	1 (0 to 15; 0%)	1 (0 to 2; 3%)	0·0068

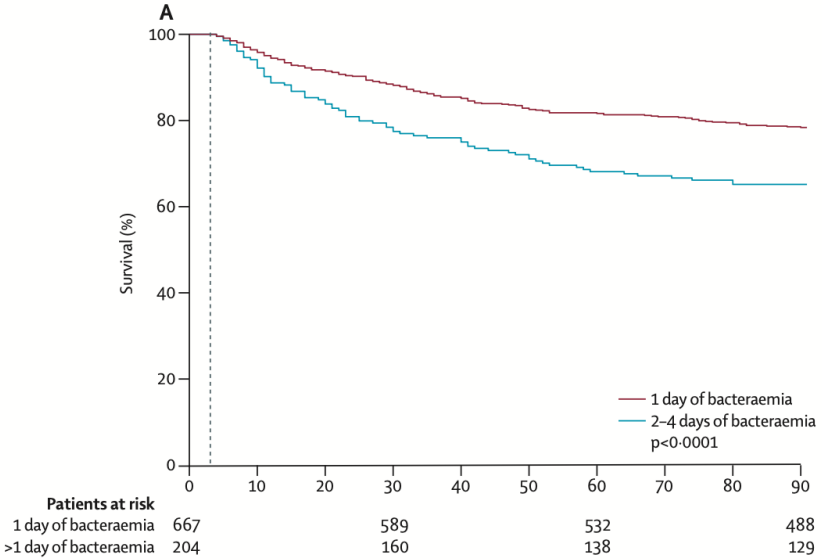
Data are n (%), n (%; % missing), median (IQR), or median (IQR; percentage missing). *Not evident at initial clinical presentation. †New focus diagnosed more than 7 days after first blood culture.

Table 2: **Outcome and management of patients grouped by the duration of bacteraemia**

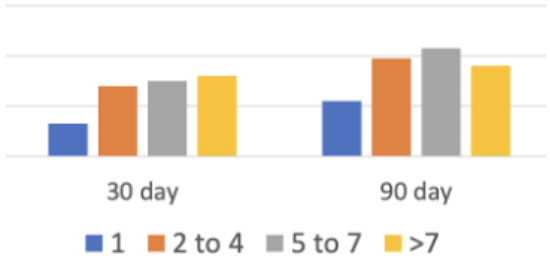
deep abscess (4%) IE (3%) bone infection (3%)

Lancet Infect Dis 2020; 20: 1409–17

Prognosis worse if BCs positive after 48h treatment



Letality according to days bacteremic *on treatment*



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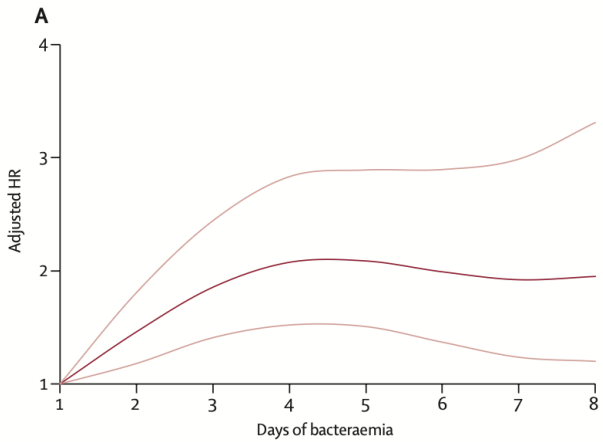
Lancet Infect Dis 2020; 20: 1409–17



B

Variable	Adjusted HR	95% CI	p value
Age	1·03	1·02–1·04	<0·0001
Charlson score	1·08	1·03–1·13	0·0005
SOFA score	1·14	1·10–1·17	<0·0001
Pneumonia	2·10	1·40–3·15	0·0003
Skin or soft tissue infection	1·63	1·06–2·51	0·024
Unknown focus	1·49	1·09–2·02	0·011
Community-acquired	0·71	0·52–0·95	0·024
Health-care associated	0·63	0·46–0·8	0·0032
Duration of bacteraemia*	..	..	<0·0001

A steady increase of the HR for 90-day mortality up to 4 days of bacteraemia

Crude 90-day mortality increased from **22%** (148 of 672) with 1 day of bacteraemia, to **39%** (85 of 218) with 2–4 days, **43%** (30 of 69) with 5–7 days, and **36%** (10 of 28) with more than 7 days of bacteraemia

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Lancet Infect Dis 2020; 20: 1409–17

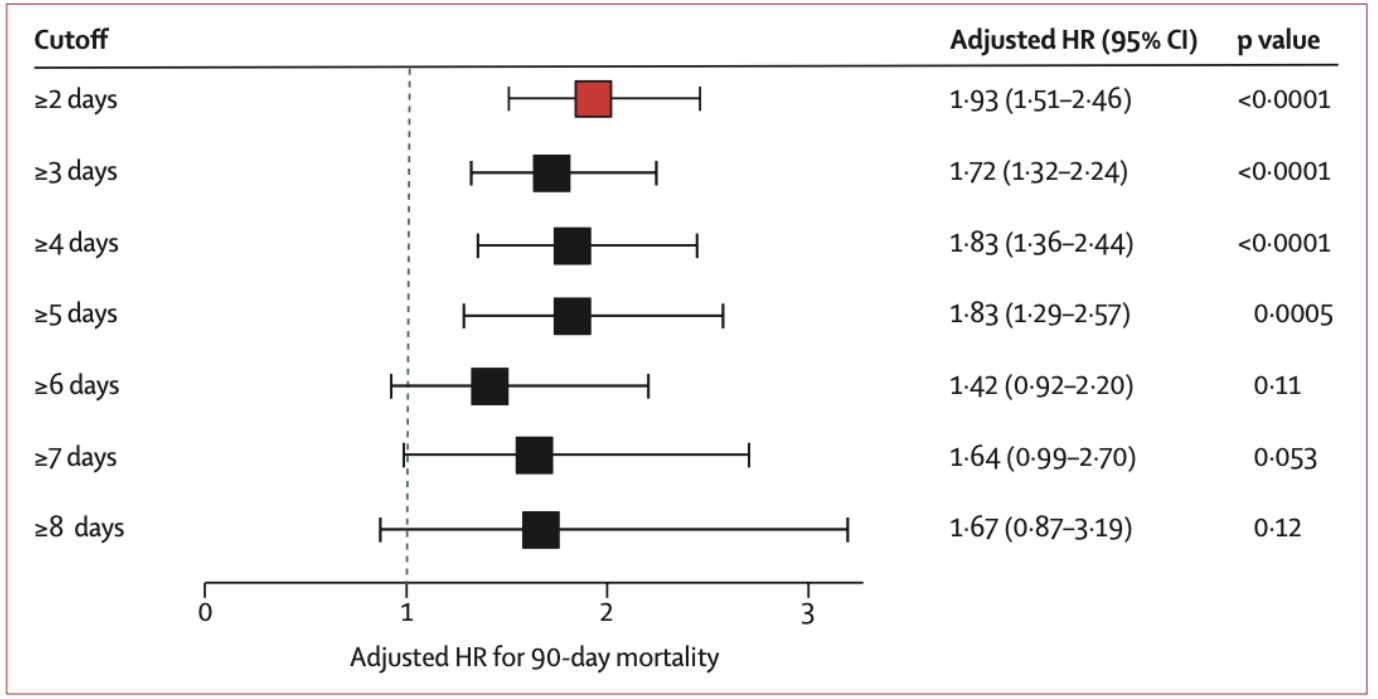

Figure 4: **Comparison of adjusted HR for 90 day-mortality with different cutoffs for persistent bacteraemia**
Data are based on the model presented in figure 3B. The red box indicates the proposed cutoff. HR=hazard ratio.

The second day of bacteraemia after initiation of active antibiotic treatment was the most pronounced and earliest cutoff that significantly differed between surviving patients and those who died

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SAB - IE

- To find the source and potential sites of metastatic infection represents a cornestone in the managment of SAB
- 10-20% of SAB episodes is complicated by infective endocarditis (IE)
- 40% of SAB-IE occurs in patients without known predisposing risk factors for IE and typical signs of endocarditis
- In clinical practice, TTE is usually obtained first; TEE is preferred but not mandatory (IDSA)
- Whether pts with SAB who do not have findings suggestive of IE on TTE should undergo TEE is an area of ongoing controversy
- The increased sensitivity of TEE must be balanced with its increased costs and potential complications (perforation 1 in 5000 pts)

SAB and TEE

- Prosthetic heart valve or other cardiac device
- Positive follow-up blood cultures >48 hrs after star of active antibiotic therapy
- Community acquisition
- Predisposing heart valve abnormality (including previous endocarditis)
- Active injection drug use
- >1 non contiguous foci of infection
- Immunodepression? Other risk factor?

IDSA

Prediction Rules for Ruling Out Endocarditis in Patients With *Staphylococcus aureus* Bacteremia

Clinical Infectious Diseases 2022;74(8):1442–9

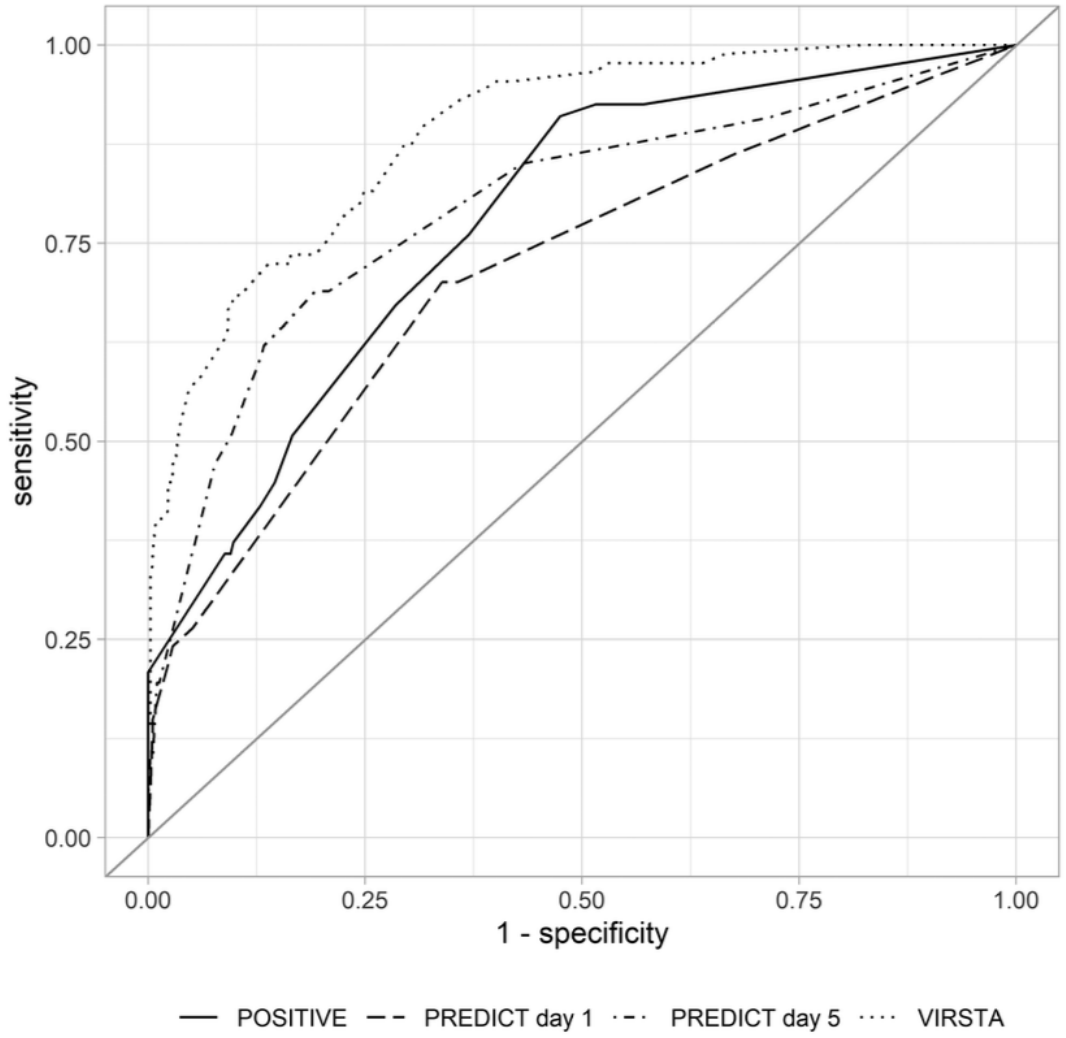
Thomas W. van der Vaart,[1,2,©] Jan M. Prins,[2] Robin Soetekouw,[3] Gitte van Twillert,[4] Jan Veenstra,[5] Bjorn L. Herpers,[6] Wouter Rozemeijer,[7] Rogier R. Jansen,[8] Marc J. M. Bonten,[1,9] and Jan T. M. van der Meer[2]

[1]Julius Center for Health Sciences and Primary Care, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands; [2]Department of Internal Medicine, Division of Infectious Diseases, Amsterdam UMC, University of Amsterdam, Amsterdam, The Netherlands; [3]Department of Internal Medicine, Spaarne Gasthuis, Haarlem, The Netherlands; [4]Department of Internal Medicine, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; [5]Department of Internal Medicine, OLVG, Amsterdam, The Netherlands; [6]Department of Medical Microbiology, Spaarne Gasthuis, Haarlem, The Netherlands; [7]Department of Medical Microbiology, Noordwest Ziekenhuisgroep, Alkmaar, The Netherlands; [8]Department of Medical Microbiology, OLVG, Amsterdam, The Netherlands; and [9]Department of Medical Microbiology, University Medical Center Utrecht, Utrecht University, Utrecht, The Netherlands

Table 1. Overview of POSITIVE, PREDICT, and VIRSTA Scores

POSITIVE Cutoff: >4		PREDICT Cutoff: ≥2 (for Day 5 Score)		VIRSTA Cutoff: ≥3	
Item	Points Assigned	Item	Points Assigned	Item	Points Assigned
TTP <9 h	5	ICD	2	Cerebral or peripheral emboli	5
TTP 9–11 h	3	Permanent pacemaker	3	Meningitis	5
TTP 11–13 h	2	Community acquisition	2	Permanent intracardiac device or previous IE	4
IV drug use	3	Healthcare acquisition	1	Preexisting native valve disease[a]	3
Vascular phenomena[b]	6	Positive culture after 72 h	2	IV drug use	4
Predisposing heart disease[c]	5			Positive culture after 48 h	3
				Community or healthcare-associated bacteremia	2
				Severe sepsis or septic shock	1
				C-reactive protein >190 mg/L	1

Score	Sensitivity (% + 95% CI)	Specificity (% + 95% CI)	Negative Predictive Value (% + 95% CI)	Positive Predictive Value (% + 95% CI)	AUC
POSITIVE[a]	77.6 (65.8–86.9)	63.1 (57.3–68.6)	92.5 (87.9–95.8)	32.3 (25.1–40.1)	77.8 (71.9–83.7)
PREDICT day 1	22.9 (14.6–33.5)	97.4 (95.3–98.8)	85.0 (81.4–88.2)	66.7 (47.2–82.7)	71.4 (65.2–77.5)
PREDICT day 5	85.1 (75.8–91.8)	56.9 (51.8–61.9)	94.5 (90.7–97.0)	30.5 (24.7–36.8)	79.7 (73.9–85.4)
VIRSTA	98.9 (95.7–100)	35.7 (30.8–40.6)	99.3 (94.9–100)	25.5 (20.7–30.3)	88.9 (85.3–92.5)



VIRSTA :

1) has the highest sensitivity and NPV

2) It also classified 70% of SAB patients as high risk, and thus having an indication for TEE

3) Implementing VIRSTA would mean an increase of 45.3% in TEEs necessary

AIM:
identify patients for whom treatment was adjusted due to the results of [18F]FDG-PET/CT, and
assessed concordance of [18F]FDG-PET/CT and clinical diagnosis for infected prosthetic material.

Methods:
Retrospective single-center cohort study,
Pts with SAB between 2013 and 2020
one [18F]FDG-PET/CT scan was performed
antibiotic treatment was planned for ≥ 6 weeks prior to [18F] FDG-PET/CT.

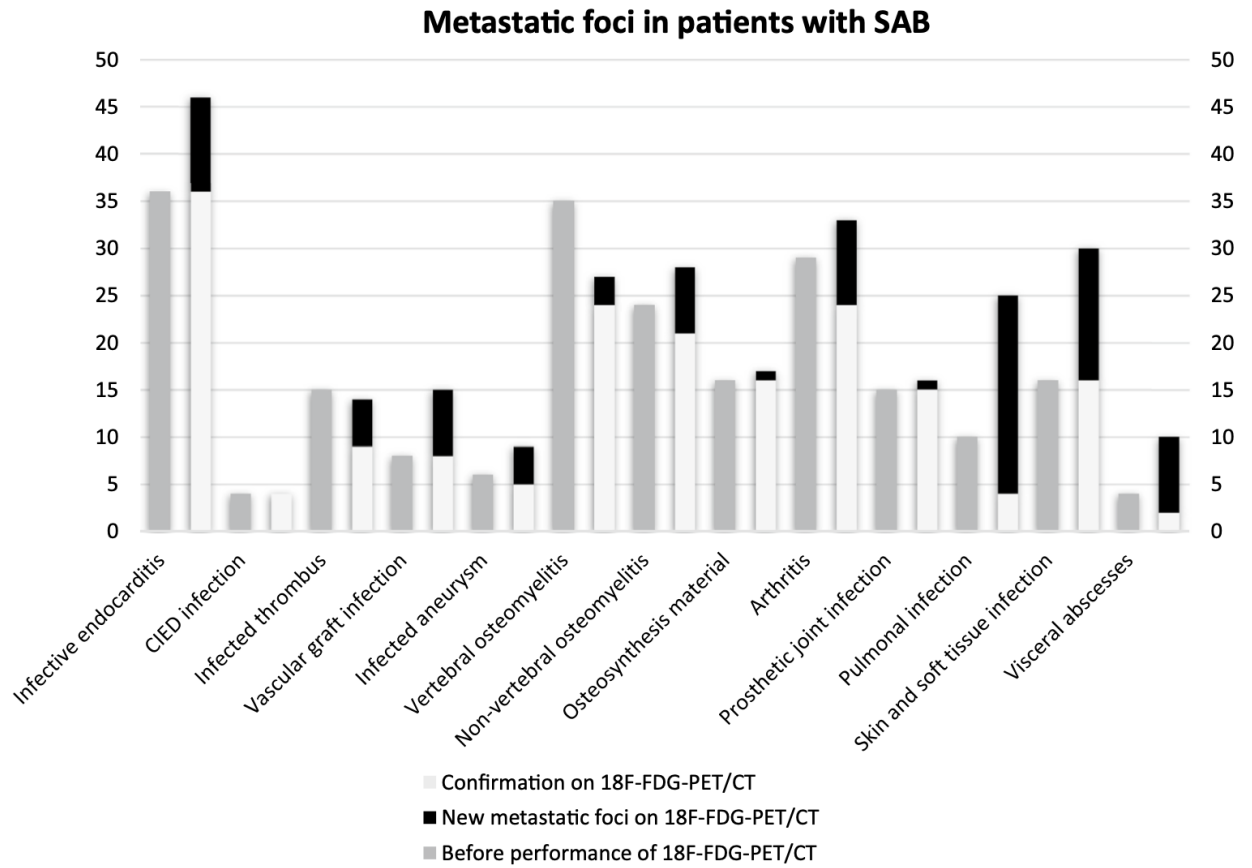
Results:
132 patients included

High sensitivity of [18F]FDG-PET/CT for detection of additional infectious foci (52,3%)
In only 16.7% of SAB [18F] FDG-PET/CT because of known changed the original treatment plan
It can be safely omitted in pts who are clinically stable and whose therapy is planned for ≥6 weeks

ORIGINAL PAPER

Individualizing the use of [^{18}F]FDG-PET/CT in patients with complicated *Staphylococcus aureus* bacteremia: experiences from a tertiary care center

Eline J. van Leerdam[1] · Michelle Gompelman[1,5] · Renée A. M. Tuinte[1] · Erik H. J. G. Aarntzen[2] · Marvin A. H. Berrevoets[3] · Ianthe Maat[4] · Chantal P. Bleeker-Rovers[1] · Reinout van Crevel[1] · Jaap ten Oever[1] · Ilse J. E. Kouijzer[1]



Infection (2022) 50:491–498

Clinical Infectious Diseases
MAJOR ARTICLE

Integration of FDG-PET/CT in the Diagnostic Workup for *Staphylococcus aureus* Bacteremia: A Prospective Interventional Matched-cohort Study

Nesrin Ghanem-Zoubi,[1,2,a] Olga Kagna,[3,a] Jawad Abu-Elhija,[4] Mona Mustafa-Hellou,[4] Majd Qasum,[5] Zohar Keidar,[2,3] and Mical Paul[1,2]

Methods:
matched-cohort study pts with SAB
FDG-PET/CT 7–14 days after diagnosis (intervention group).
Matched group (no FDG-PET/CT) by age, Charlson score, methicillin susceptibility, and survival duration to FDG-PET/CT.

Primary outcome
90-day mortality.

Results:
149 pts intervention group
150 matched pts

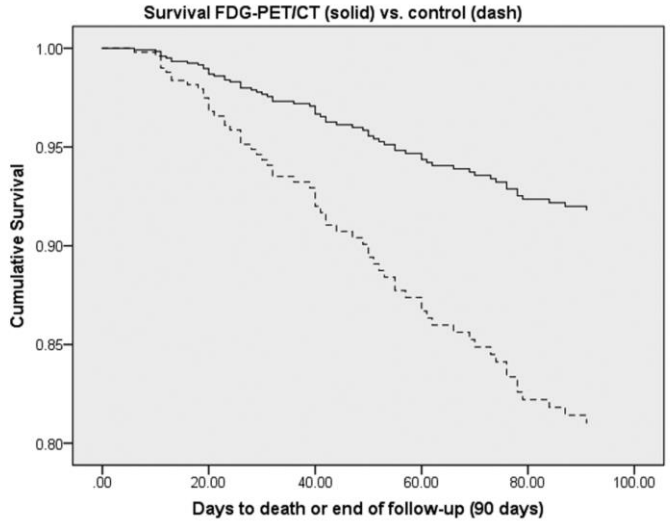


Table 1. Infectious Sites Detected by FDG-PET/CT in the Intervention Group According to Clinical Suspicion Before FDG-PET/CT

		Results According to FDG-PET/CT			
Site of Infection	Suspected Before FDG-PET/CT	Excluded by FDG-PET/CT	Confirmed by FDG-PET/CT	Newly Diagnosed by FDG-PET/CT	Number of Cases (% of Total Cases) as Detected by FDG-PET/CT
Bone and joint	37	10	27	31	58 (38.4)
Skin and soft tissue	42	22	20	15	35 (23.1)
Muscles	…	…	…	16	16 (10.6)
Vascular-extracardiac	4	1	3	17	20 (13.2)
Cardiac	17	10	7	2	9 (5.9)
Internal organs (abdomen, pelvis, thorax)	…	…	…	9	9 (5.9)
Lungs	9	5	4	28	32 (21.1)
No focus identified	27	16	11	27	38 (25.1)

N = 151. Sum of diagnoses is >100% due to multiple foci detected.
Abbreviation: FDG-PET/CT, fluorodeoxyglucose–positron emission tomography/computed tomography.

Integrating FDG-PET/CT in the diagnostic work-up of SAB seems to improve survival. The benefit might be mediated by infective foci detection, earlier interventions to control infection, prolongation of antimicrobial treatment, and possibly optimized antimicrobial treatment for deep infections.

TTE/TEE and 18F-FDG PET/CT Scan: summary

- TTE: on all patients with SAB
- TEE if: a) High risk
  b) Indeterminate or low quality TTE
- 18F-FDG PET/CT Scan: Clinical signs of metastatic infection, implanted prostheses, BC positive >48h, persistent fever o delayed start antibiotics
- Thoracic-abdominal CT: alternative
- Spinal MR: alternative

Agenda

- Epidemiology and lethality
- Clinical Characteristics: High Risk and Low Risk
- Persistent *Staphilococcus aureus* Bacteriemia: Definition and Prognosis
- TTE, TEE and 18F-FDG PET/CT Scan : when and for which patients
- Antimicrobial Treatment: Guidelines, RCT and real world data
- Early oral switch of antimicrobial therapy
- Special patients: old patients
- Take-home massages

Clinical Infectious Diseases
MAJOR ARTICLE

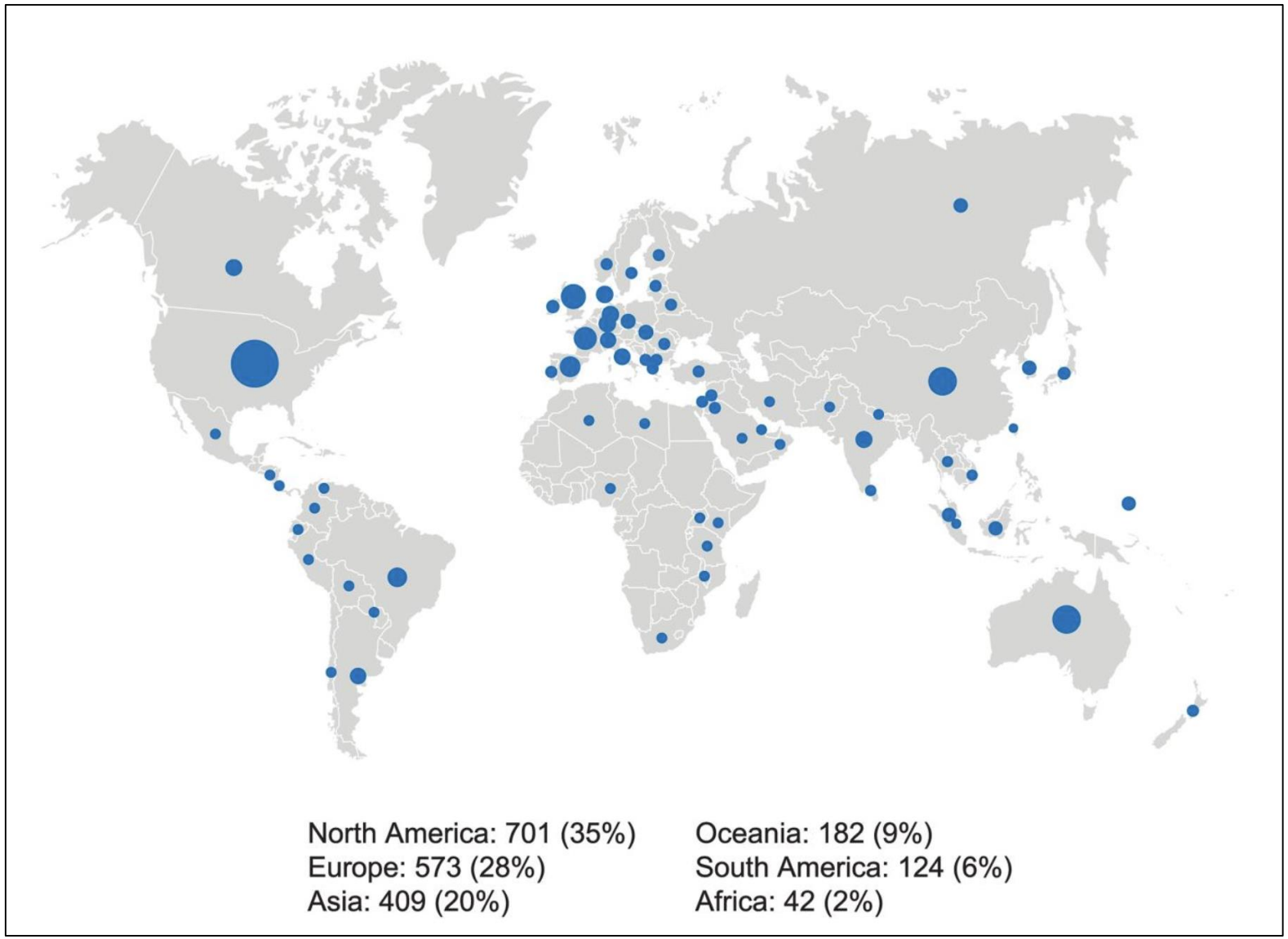
Global Differences in the Management of *Staphylococcus aureus* Bacteremia: No International Standard of Care

Annette C. Westgeest,[1,2,©] David T. P. Buis,[3] Kim C. E. Sigaloff,[3] Felicia Ruffin,[1] Leo G. Visser,[2] Yunsong Yu,[4] Emile F. Schippers,[2,5] Merel M. C. Lambregts,[2] Steven Y. C. Tong,[6,7] Mark G. J. de Boer,[2,8] and Vance G. Fowler Jr [1,9]

About SAB remain fundamentally unknown

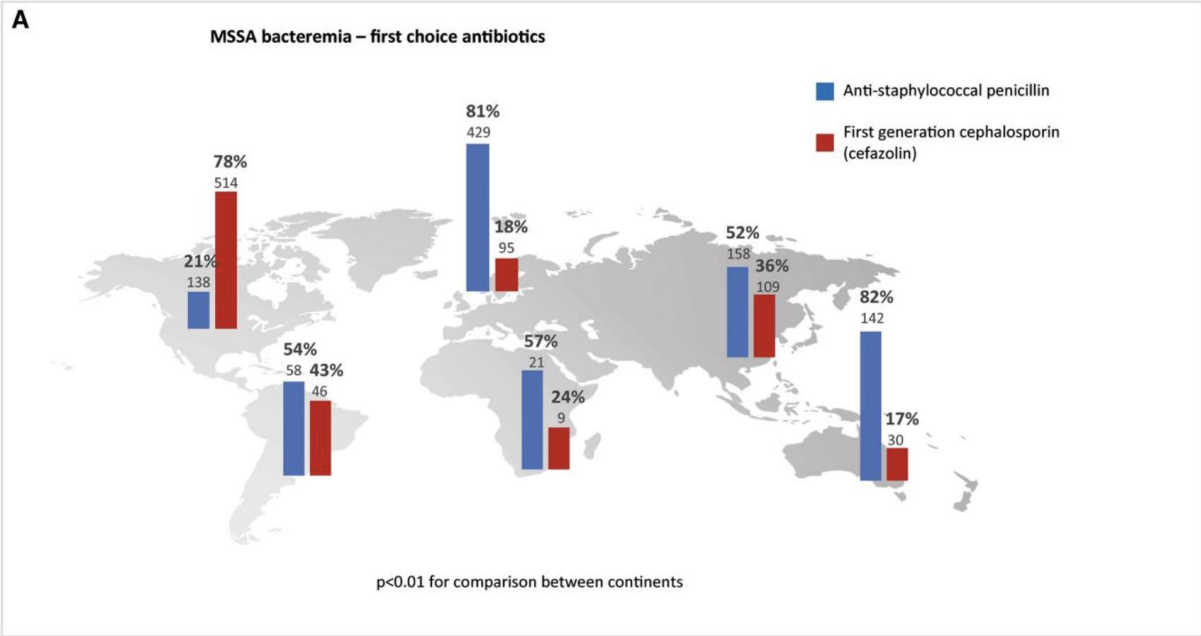
1)optimal antibiotic regimen,
2)COMBO vs MONO therapy
3)optimal treatment duration
4)definition of persistent SAB

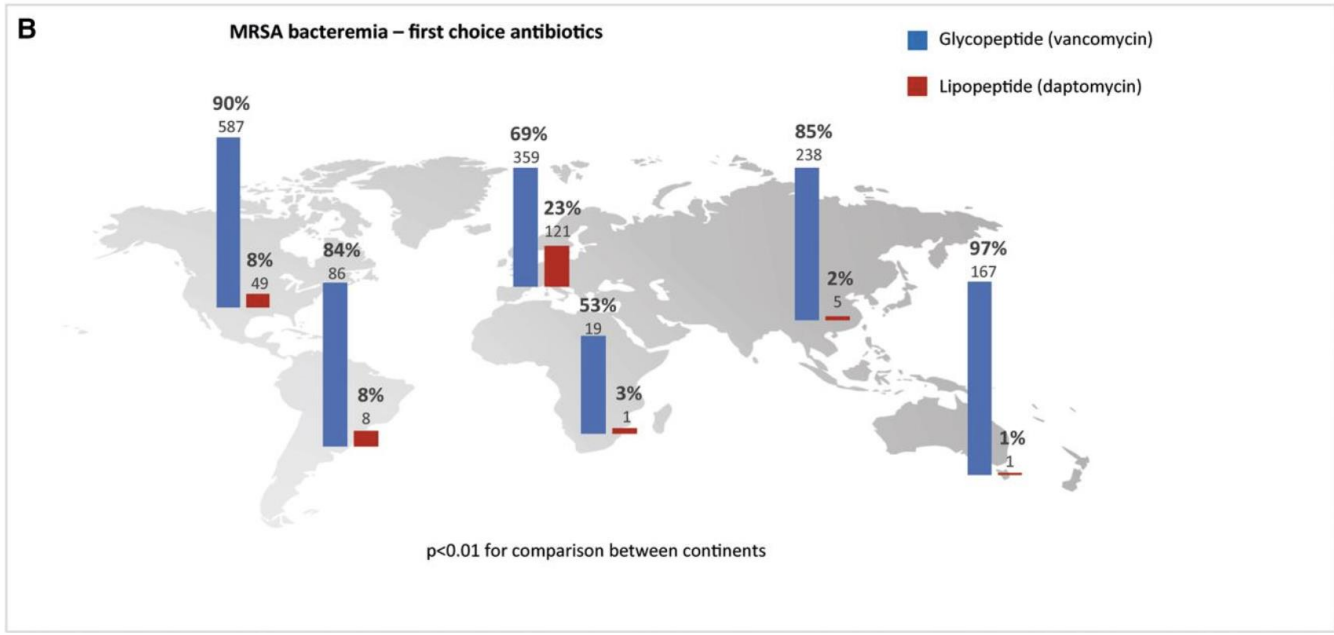
Survey: 2031 physicians from 71 different countries on 6 continents



Clinical Infectious Diseases 2023;77(8):1092–101

Antimicrobial Management of SAB

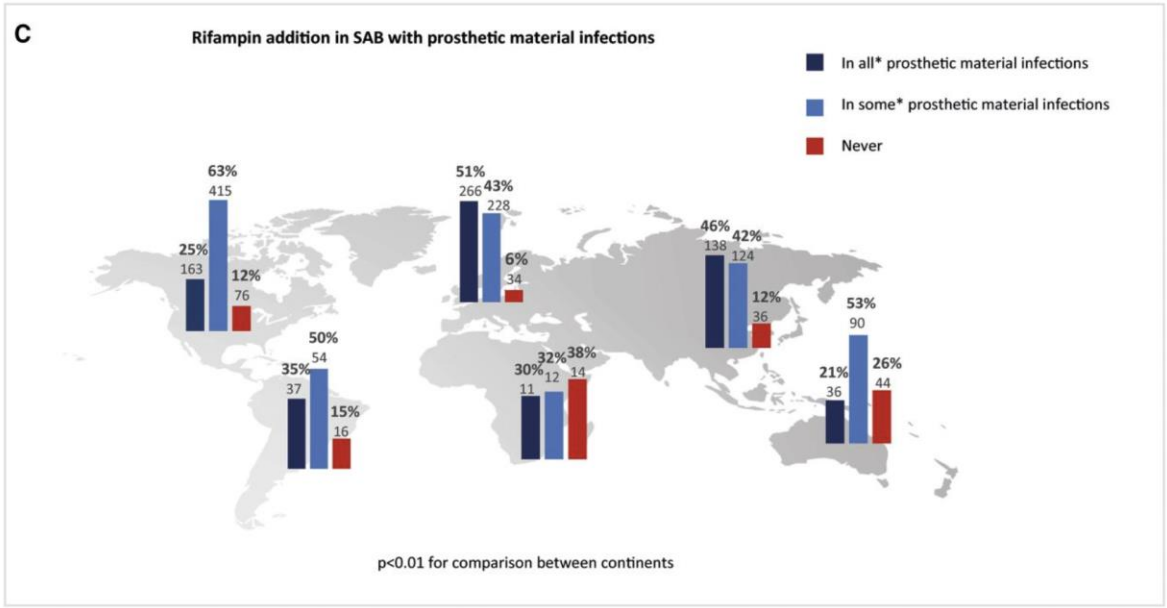


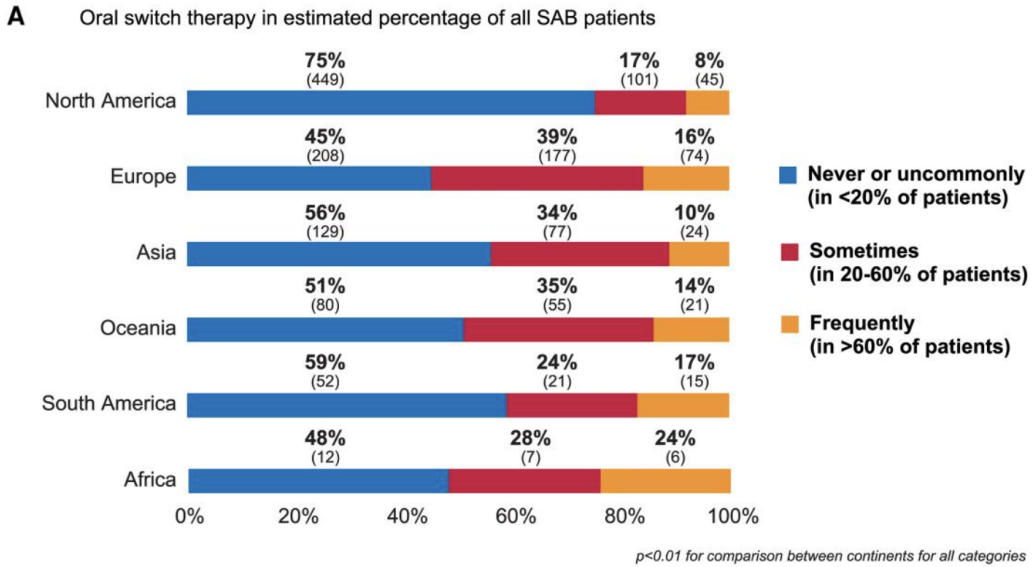


For MSSA bacteremia, cefazolin was the first-choice antibiotic treatment in North America (78% of respondents), whereas anti-staphylococcal penicillins were preferred in all other continents (51%–82%; P < .01)
For MRSA bacteremia, vancomycin was the preferred first-choice antibiotic agent in all continents, but with a broad range of 53%–97% of respondents.

Clinical Infectious Diseases 2023;77(8):1092–101

Adjunctive Rifampin and Oral Switch Therapy





Rifampin therapy in cases of SAB associated with infected prosthetic material was most frequently reported in Europe (94%)
Acceptance of oral therapy was highest in Europe (55%)

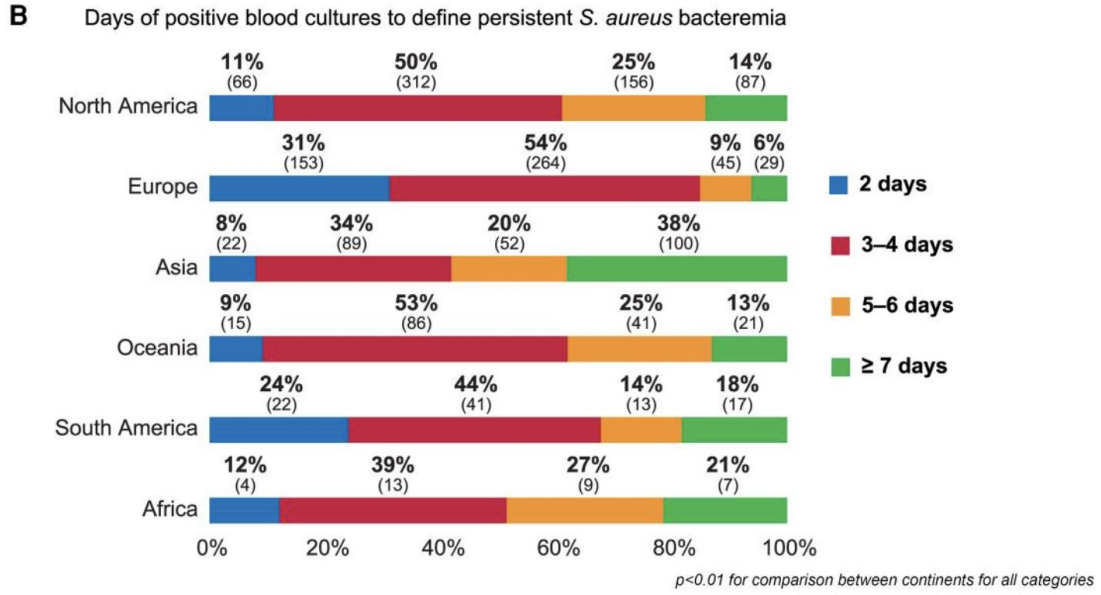
Source control and absence of a central nervous system infection were the only criteria for oral switch therapy for which there was broad agreement among respondents

Clinical Infectious Diseases 2023;77(8):1092–101

18F-FDG PET/CT Scan use and Persistent S. aureus Bacteremia Definition

	Total N = 2031	North America N = 701	Europe N = 573	Asia N = 409	Oceania N = 182	South America N = 124	Africa N = 42	*P*[+]
18F-FDG PET/CT for SAB								
PET/CT readily available	829 (55.6)	278 (48.9)	341 (78.0)	106 (46.7)	78 (51.3)	24 (28.6)	2 (9.1)	<.01
PET/CT for SAB covered by insurance	610 (42.2)	177 (33.2)	332 (77.4)	41 (18.2)	37 (24.3)	21 (25.0)	2 (9.1)	<.01
PET/CT use in some/all SAB patients	1009 (67.8)	293 (51.1)	409 (93.8)	125 (57.0)	124 (82.8)	50 (61.0)	4 (12.7)	<.01
Never use PET/CT in SAB patients	479 (32.2)	281 (49.0)	27 (6.2)	96 (43.0)	26 (17.2)	32 (39.0)	17 (77.3)	<.01
Available, but never use PET/CT in SAB[b]	101 (12.2)	63 (22.7)	5 (1.5)	24 (23.1)	8 (10.3)	1 (4.2)		<.01

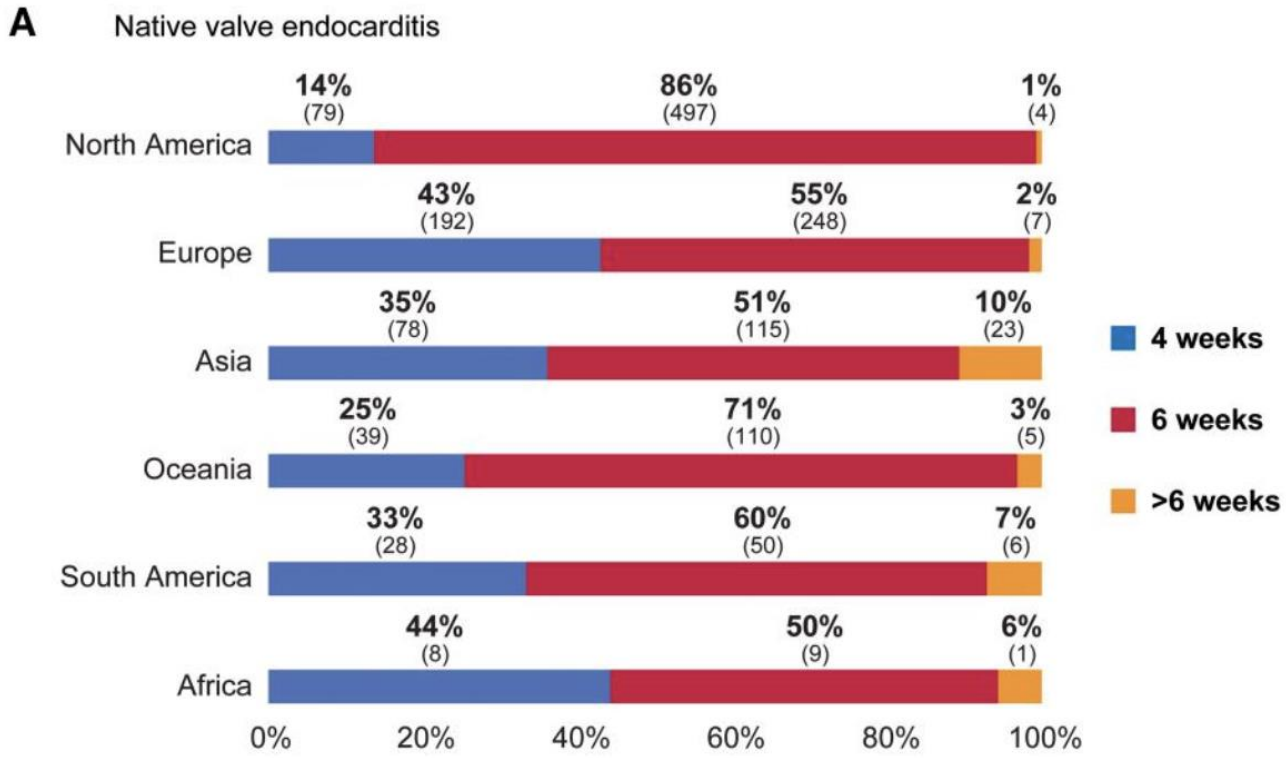
The most important and most agreed upon indication for 18F-FDG PET/CT scan in SAB was persistent bacteremia (62%–70%) of physicians

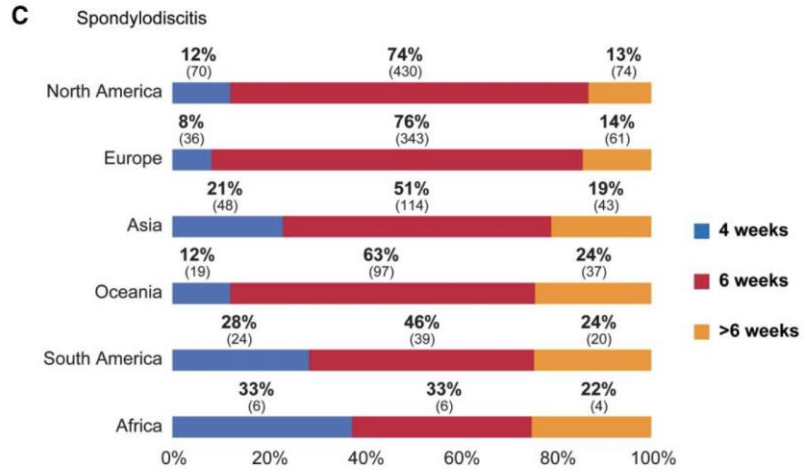


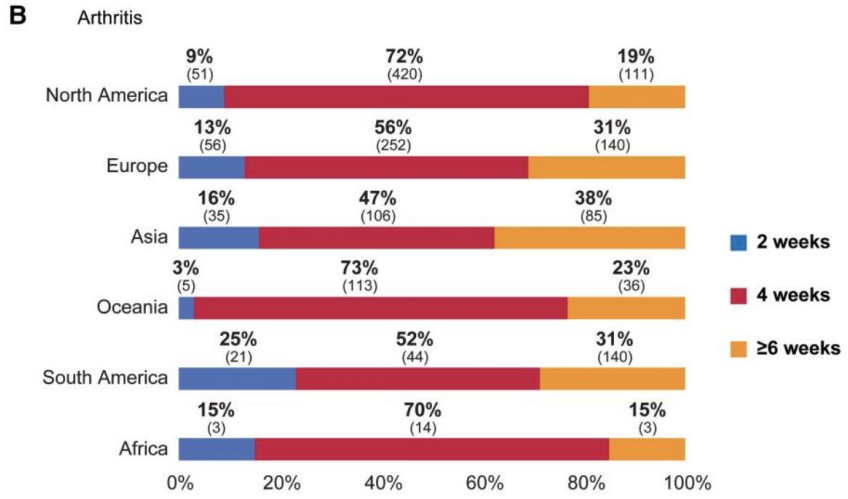
The clinical definition of persistent SAB varied widely between continents
All physicians order additional diagnostic testing in the setting of persistent SAB (79% in Africa, > 90% in all other continents), and a majority of physicians change their medical management (range 64% in Europe to 84% in North America; P < .01)

Clinical Infectious Diseases 2023;77(8):1092–101

Treatment duration







Clinical Infectious Diseases 2023;77(8):1092–101

MSSA and MRSA therapy

Drug	Recommended dose	Considerations	Common adverse effects (1%-10% incidence)
For methicillin-susceptible *S aureus*[b]			
Cefazolin	2 g every 8 h	Use 2 g every 6 h for critically unwell patients; may be used in most cases of nonsevere penicillin allergy Cefazolin associated with less toxicity and lower mortality than antistaphylococcal penicillins in observational studies	Gastrointestinal (diarrhea, nausea, vomiting)
Flucloxacillin	2 g every 6 h	Use 2 g every 4 h for critically unwell patients and for infective endocarditis	Gastrointestinal (diarrhea, nausea, vomiting), local injection site thrombophlebitis, acute kidney toxicity, drug allergy
Cloxacillin	2 g every 4 h		
Nafcillin	2 g every 4 h		
Oxacillin	2 g every 4 h		
Benzylpenicillin	2.4 g (4 million U) every 4 h	Only for *S aureus* isolates phenotypically confirmed as penicillin-susceptible with disk diffusion testing	Drug allergy
For methicillin-resistant *S aureus*			
Vancomycin	Loading dose of 20-35 mg/kg (maximum, 3 g), then 15-20 mg/kg (maximum, 2 g) every 12 h[c]	AUC-guided dosing is recommended, aiming for an AUC of 400-600[d] When trough level-guided dosing is used, levels of 15-20 mg/L are effective but associated with increased kidney toxicity[d]	Vancomycin infusion reaction, acute kidney toxicity, ototoxicity
Daptomycin	6-10 mg/kg once daily	FDA-approved dose is 6 mg/kg once daily; however, many clinicians favor higher dosing of 8 to 10 mg/kg once daily because daptomycin exhibits concentration-dependent killing Do not use for methicillin-resistant *S aureus* pneumonia	Creatinine kinase elevation; eosinophilic pneumonia
Ceftobiprole	500 mg every 6 h for 8 d, then 500 mg every 8 h		Gastrointestinal (diarrhea, nausea, vomiting)

Comparative Effectiveness of Beta-Lactams Versus Vancomycin for Treatment of Methicillin-Susceptible *Staphylococcus aureus* Bloodstream Infections Among 122 Hospitals

Jennifer S. McDanel,[1,2,3] Eli N. Perencevich,[1,2,3] Daniel J. Diekema,[2,4,5] Loreen A. Herwaldt,[1,2,5] Tara C. Smith,[1,a] Elizabeth A. Chrischilles,[1] Jeffrey D. Dawson,[6] Lan Jiang,[3] Michihiko Goto,[2,3] and Marin L. Schweizer[1,2,3]

[1]Department of Epidemiology, College of Public Health, [2]Department of Internal Medicine, Carver College of Medicine, University of Iowa, [3]Iowa City Veterans Affairs Health Care System, [4]Department of Pathology, Carver College of Medicine, University of Iowa, [5]Clinical Quality, Safety, and Performance Improvement, University of Iowa Hospitals and Clinics, and [6]Department of Biostatistics, College of Public Health, University of Iowa, Iowa City

Clinical Infectious Diseases 2015;61(3):361—7

Methods:
Retrospective cohort study 2003-2010
>18 pts with SAB (MSSA)
Primary oucome:
30-day mortality vancomycin vs beta-lactam therapy
Results:
Beta-Lactam (2659 pts) Vancomycin (3125 pts)
Empiric therapy with a beta-lactam had similar mortality compared with those who received vancomycin (HR, 1.03; 95% CI, .89-1.20)
Definitive therapy with a beta-lactam had 35% lower mortality compared with patients who received vancomycin (HR, 0.65; 95% CI, .52-.80)

Characteristic	Patients Who Received Beta-Lactams[a] (N = 4698)	Patients Who Received Vancomycin[a] (N = 935)	*P* Value
Gender, male	4598 (98)	909 (97)	.218
Age, >64 y	2261 (48)	470 (50)	.232
Acute physiology and chronic health evaluation III score, >33	2475 (53)	437 (47)	.001
Charlson comorbidity index, median (range[b]) score	2 (1–3)	2 (1–3)	.199
Diabetes	1671 (36)	331 (35)	.922
Moderate or severe liver disease	199 (4)	28 (3)	.078
Additional infections			
Pneumonia	926 (20)	112 (12)	<.001
Osteomyelitis	498 (11)	40 (4)	<.001
Endocarditis	189 (4)	21 (2)	.009
Dialysis/end stage renal disease[c]	473 (10)	128 (14)	.001
Community-onset infection[d]	3582 (76)	671 (72)	.004
Prior hospitalization	2632 (56)	572 (61)	.004
Beta-lactam allergy	595 (13)	440 (47)	<.001
Prior methicillin-resistant *Staphylococcus aureus* nasal colonization	204 (4)	57 (6)	.020
Year of admission			.133
2003	674 (14)	126 (13)	
2004	644 (14)	117 (13)	
2005	602 (13)	133 (14)	
2006	563 (12)	125 (13)	
2007	542 (12)	111 (12)	
2008	587 (12)	118 (13)	
2009	525 (11)	120 (13)	
2010	561 (12)	85 (9)	
Facility type[e]			.001
1a (most complex)	2186 (47)	439 (47)	
1b	933 (20)	236 (25)	
1c	739 (16)	118 (13)	
2	514 (11)	90 (10)	
3 (least complex)	125 (3)	19 (2)	
Length of stay in the hospital, median (range[b]) days[f]	12 (8–21)	8 (6–13)	<.001
30-day mortality[g]	679 (14)	112 (12)	.047

For patients with MSSA bloodstream infections, beta-lactams are superior to vancomycin for definitive therapy but not for empiric treatment.

Systematic review

Cefazolin versus anti-staphylococcal penicillins for the treatment of patients with *Staphylococcus aureus* bacteraemia

S. Weis [1, 2, 3, *], M. Kesselmeier [2, 4], J.S. Davis [5, 6], A.M. Morris [7], S. Lee [8], A. Scherag [2, 4, 9], S. Hagel [1, 2, †], M.W. Pletz [1, †]

Methods:

Meta-analysis 14 studies (11000 pts)

Aim

To compare cefazolin vs ASPs for MSSA treatment

Results

Primary outcome:

Lower 90-day mortality rate RR 0.71, 95% CI (0.50, 1.02)

Secondary outcomes:

Lower 30-day mortality rate RR 0.70, 95% CI (0.54, 0.91)

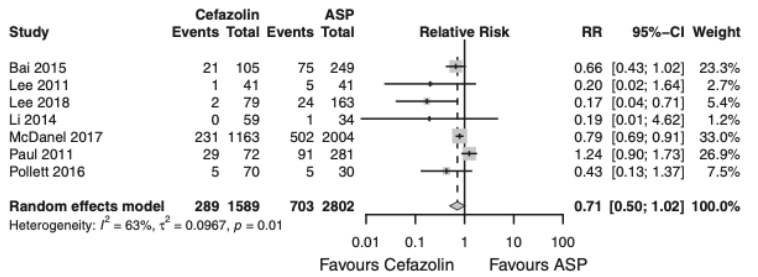
Less nephrotoxicity RR 0.36, 95% CI (0.21, 0.59)

Treatment failure/relapse RR 0.84, 95%CI (0.59, 1.18) (moderate heterogeneity)

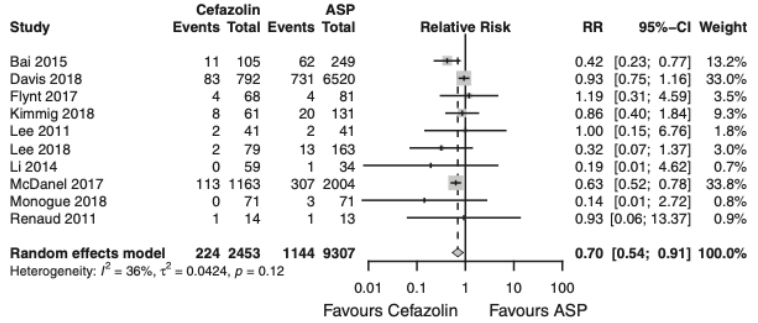
Cefazolin was not associated with increased 90-day mortality and associated with a better outcome (30-day mortality and nephrotoxicity) compared to treatment with ASP

Weis S. Clin Microbiol Infect.2019;25(7):818-827

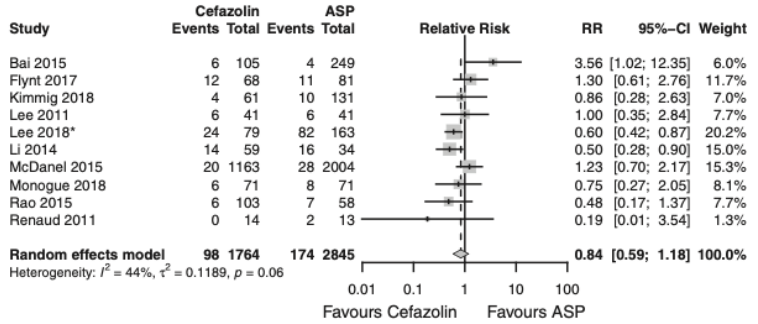
(a) 90−day all−cause mortality



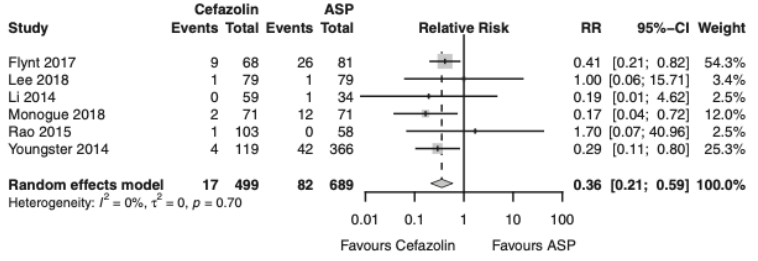
(b) 30−day all−cause mortality



(c) Treatment failure / relapse



(d) Nephrotoxicity



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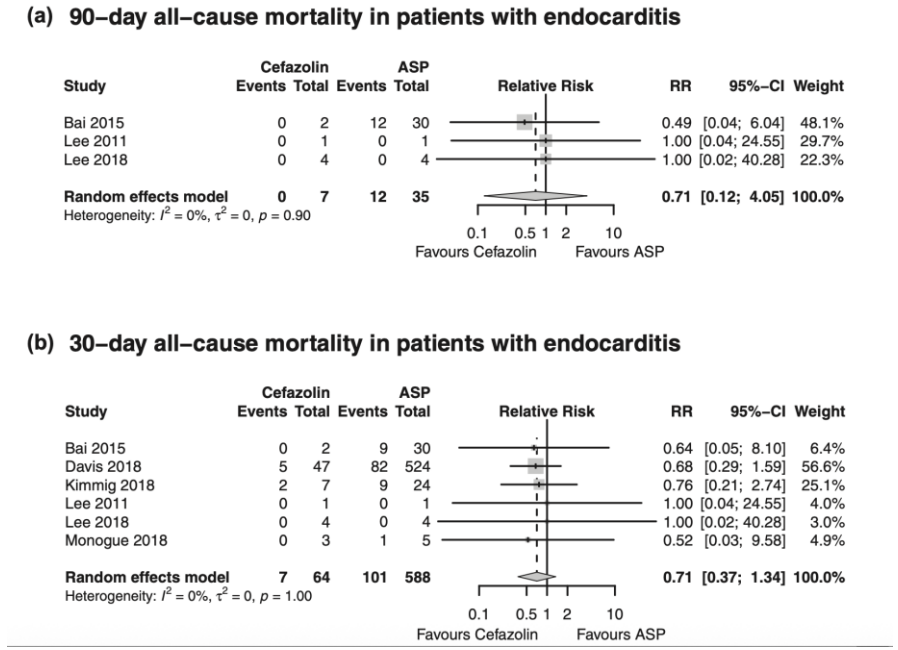
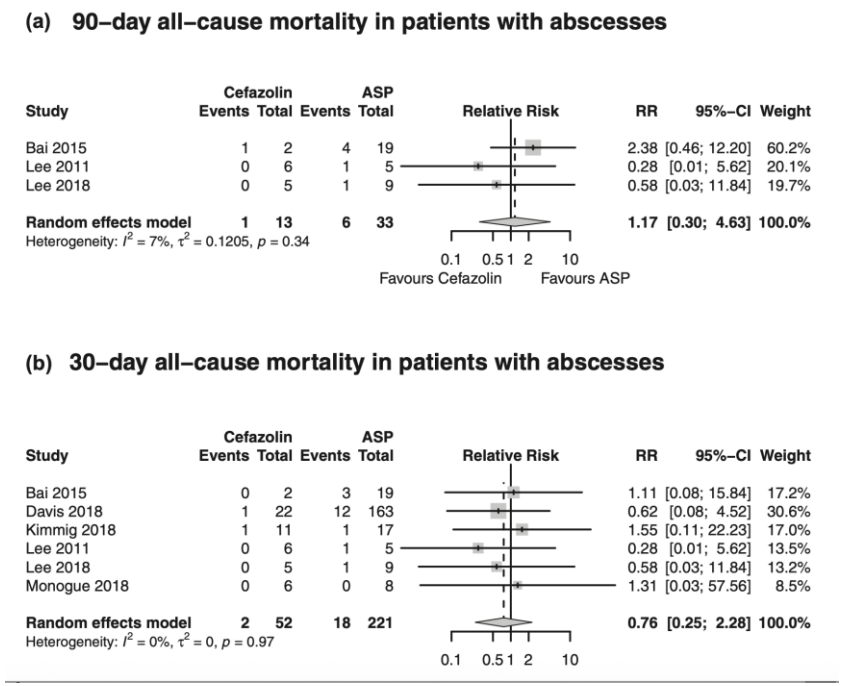
Studies in patients with high pathogen inoculum

Cefazolin treatment was not associated with increased mortality as compared to treatment with ASP in the outcome of patients with potential high pathogen load



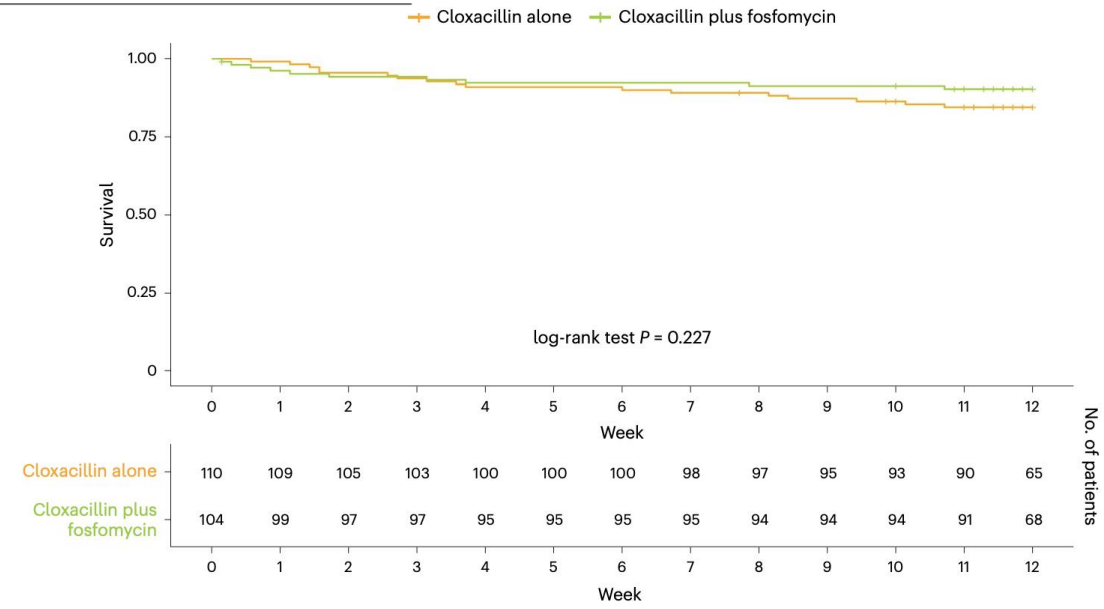


Weis S. Clin Microbiol Infect.2019;25(7):818-827

Cloxacillin plus fosfomycin versus cloxacillin alone for methicillin-susceptible *Staphylococcus aureus* bacteremia: a randomized trial

Grillo S. Nature Medicine 2023; 29:2518–2525

Methods:
RCT
>18y with MSSA BSI
Randomised (1:1) for 7 days
cloxacillin 2gr every 4 h alone vs
cloxacillin 2gr every 4 h+ fosfomycin 3gr every 6h
Primary outcome
Treatment success at day 7 (`alive, stable improved qSOFA, afebrile and with negative blood cultures for MSSA`)
Results:
105 pts cloxacillin plus fosfomycin
110 pts cloxacillin alone
persistent bacteremia at day 3,
was less common in the combination arm



Cloxacillin plus fosfomycin did not achieve better treatment success at day 7 of therapy than cloxacillin alone in MSSA bacteremia

Article

The Effectiveness of Combination Therapy for Treating Methicillin-Susceptible *Staphylococcus aureus* Bacteremia: A Systematic Literature Review and a Meta-Analysis

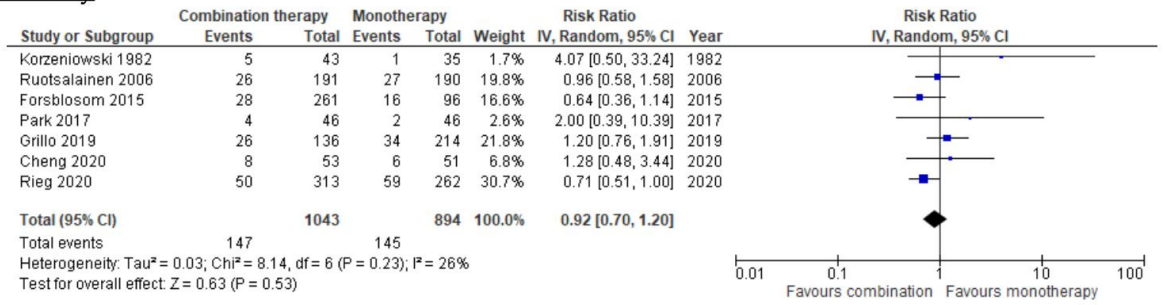
Sara Grillo [1,†], Mireia Puig-Asensio [1,2,3,*,†], Marin L. Schweizer [3,4], Guillermo Cuervo [1,2], Isabel Oriol [5], Miquel Pujol [1,2] and Jordi Carratalà [1,2,6]

Combination therapy not only did not decrease mortality in patients with MSSA bacteremia, but also increased the risk of adverse events.

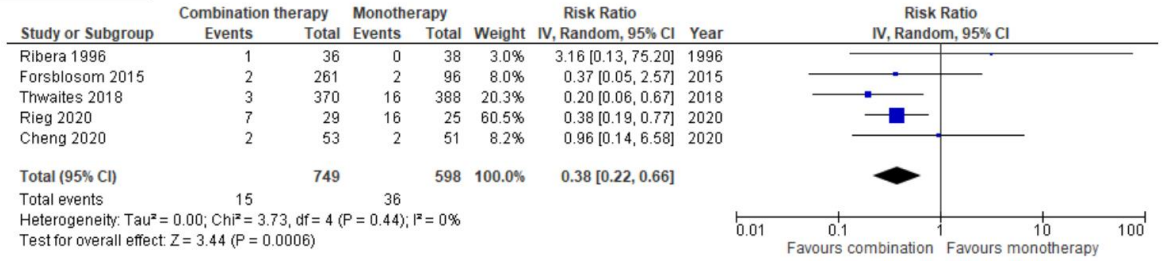
Combination therapy may reduce the risk of relapse, but additional high-quality studies are needed

Methods:
meta-analysis (12 studies)
AIM:
evaluate the effectiveness of combination therapy for treating MSSA bacteremia
Primary outcome: all-cause mortality.
Secondary outcomes: persistent bacteremia, duration of bacteremia, relapse, and adverse events.
Results:
COMBO did not significantly reduce
30-day mortality (OR 0.92, 95% CI, 0.70–1.20) and
90-day mortality (OR 0.89, 95% CI,0.74–1.06)
COMBO decreased the risk of relapse (OR 0.38, 95% CI, 0.22–0.66), but this benefit was not maintained when pooling RCTs (OR 0.54, 95% CI, 0.12–2.51)
COMBO increased risk of AEs (pRR 1.74, 95% CI, 1.31–2.31).

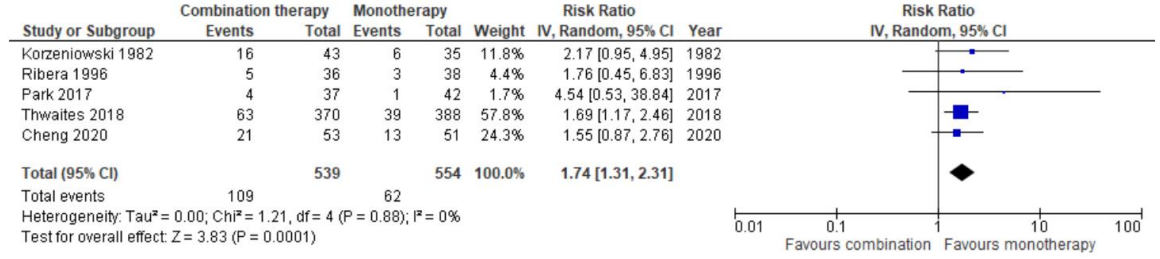
30-day mortality



Relapse or recurrence



Drug-adverse events



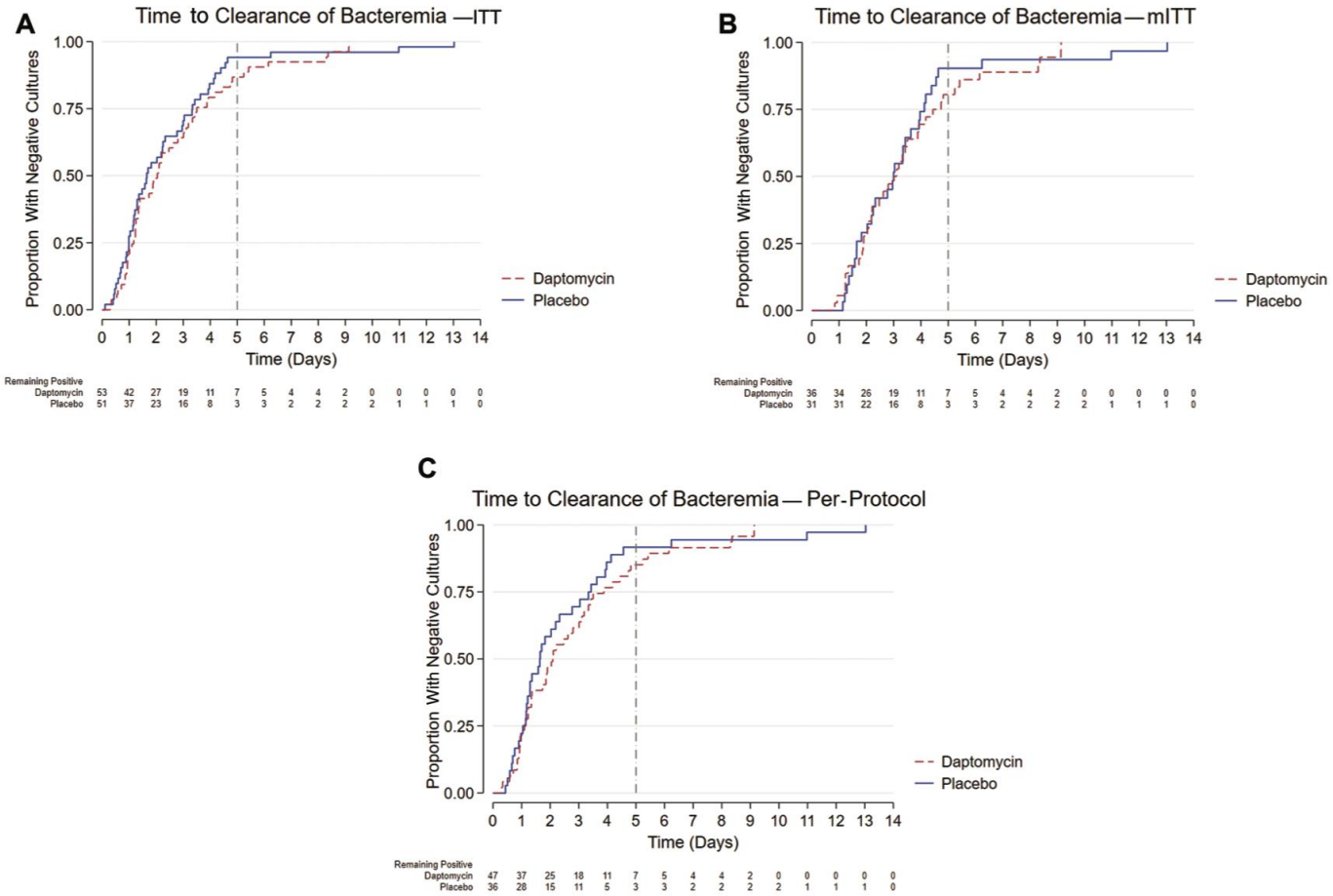
Adjunctive Daptomycin in the Treatment of Methicillin-susceptible *Staphylococcus aureus* Bacteremia: A Randomized, Controlled Trial

Matthew P. Cheng,[1,a] Alexander Lawandi,[2,a] Guillaume Butler-Laporte,[2,a] Samuel De l'Étoile-Morel,[2] Katryn Paquette,[3] and Todd C. Lee[2,4,5]

[1]Division of Infectious Diseases, Department of Medicine, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA, [2]Division of Infectious Diseases, Department of Medicine, McGill University, Montreal, Quebec, Canada, [3]Division of Neonatology, Montreal Children's Hospital, McGill University, Montreal, Quebec, Canada, [4]Research Institute of the McGill University Health Centre, Montreal, Quebec, Canada, and [5]Clinical Practice Assessment Unit, Department of Medicine, McGill University, Montreal, Quebec, Canada

Among patients with MSSA BSIs, the administration of adjunctive daptomycin therapy to standard-of-care treatment did not shorten the duration of bacteremia and should not be routinely considered

Methods:
RCT
>18 y with MSSA BSI
Treated with cefazolin or cloxacillin
Intervention:
5-day course of daptomycin or placebo.
Primary outcome:
duration of MSSA BSI in days
Results:
The median duration of bacteremia was 2.04 days DAP patients vs 1.65 days PLB pts (absolute difference, 0.39 days; P=.40).
For bacteriemic pts at enrollement 3.06 days DAP patients vs 3.00 days PLB pts (absolute difference, 0.06 days; P=.77).



Clinical Infectious Diseases 2021;72(9):e196–203

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)**

Methods

RCT double-blind, placebo-controlled trial

adults (≥18 years) with S aureus bacteraemia

≤96 h of active antibiotic therapy randomised (1:1) to receive 2 weeks of adjunctive rifampicin (600 mg or 900 mg /day) vs placebo

Primary outcome:

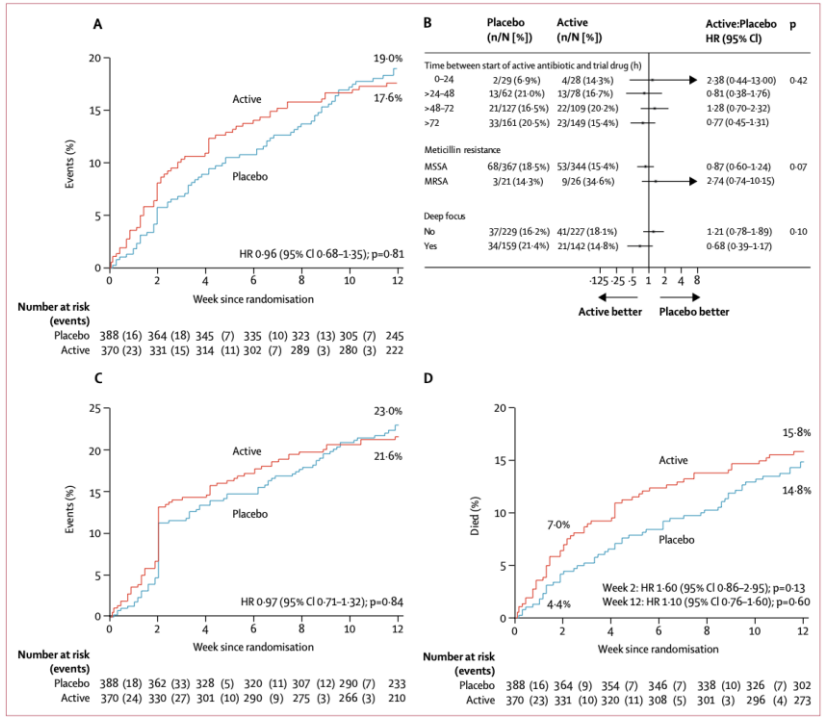
Time to bacteriologically failure

disease recurrence, or death (all-cause), from randomisation to 12 weeks,

Results:

370 rifampicin

388 to placebo



	Bacteriological failure or recurrence			Clinical failure or recurrence			Deaths (all)	
	Placebo	Rifampicin	p value	Placebo	Rifampicin	p value	Placebo	Rifampicin
Total randomised	388	370	..	388	370	..	388	370
Total events	71 (18%)	62 (17%)	0·81	86 (22%)	76 (21%)	0·84	56 (14%)	56 (15%)
Failure	5 (1%)	4 (1%)	0·82	25 (6%)	23 (6%)	0·97	..	..
Failure due to slow resolution	3 (1%)	1 (<1%)	..	17 (4%)	10 (3%)	..	..	..
Recurrence	16 (4%)	3 (1%)	0·01	23 (6%)	8 (2%)	0·01	..	..
Death without either	50 (13%)	55 (15%)	0·30	38 (10%)	45 (12%)	0·22	..	..

From randomisation to 12 weeks, 63 (17%) participants in the rifampicin group versus 39 (10%) in the placebo group had antibiotic or trial drug-modifying adverse events (p=0·004), and 24 (6%) versus 6 (2%) had drug interactions (p=0·0005).

Lancet 2018; 391: 668–78

Continuous versus Intermittent Infusion of Oxacillin for Treatment of Infective Endocarditis Caused by Methicillin-Susceptible *Staphylococcus aureus*▽

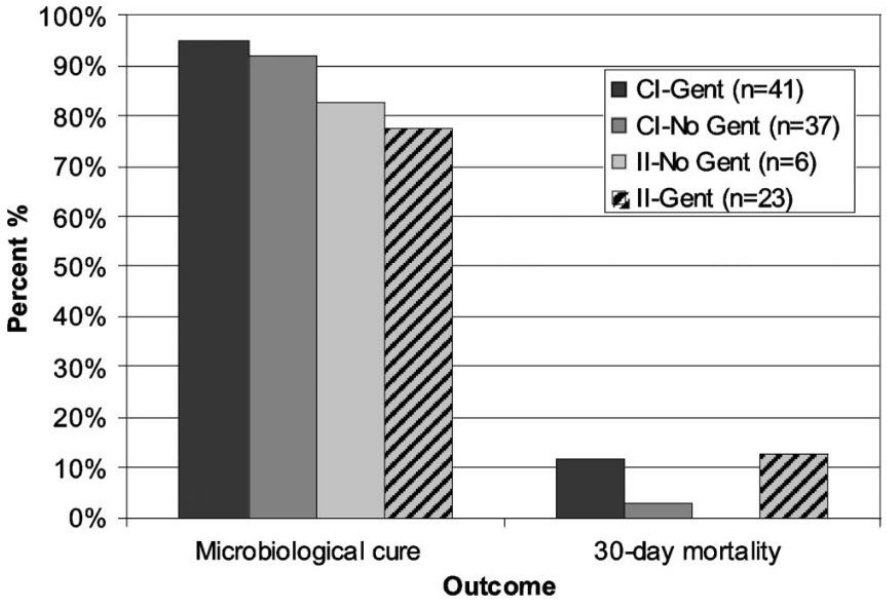
Darrel W. Hughes,[1,2,3] Christopher R. Frei,[2,3] Pamela R. Maxwell,[1,2,3] Kay Green,[1] Jan E. Patterson,[4,5] George E. Crawford,[4,5] and James S. Lewis II[1,2,3,4]*

Department of Pharmacy Services, University Health System, San Antonio, Texas[1]; The University of Texas at Austin College of Pharmacy, Austin, Texas[2]; Pharmacotherapy Education and Research Center, The University of Texas Health Science Center at San Antonio, San Antonio, Texas[3]; Department of Medicine, Division of Infectious Diseases, The University of Texas Health Science Center at San Antonio, San Antonio, Texas[4]; and South Texas Veterans Health Care System, San Antonio, Texas[5]

Received 16 September 2008/Returned for modification 30 October 2008/Accepted 18 February 2009

Methods:
Retrospective study
Pts with MSSA IE
AIM:
Evaluate Oxa-CI vs Oxa-II
Results:
107 pts (78 Oxa-CI vs 29 Oxa-II)
CI vs II groups were similar:
30-day mortality (8% versus 10%, P 0.7)
length of stay (20 versus 25 days, P 0.4)
30-day microbiological cure significant differed (94% versus 79%, P 0.03)

CI was the only indipendent variable associated with 30-day microbiological cure with oxacillin at multivariate analysis (p=0.01)



CI granted significantly higher microbiological cure rate compared to intermittent infusione (94% vs 79% p=0.03)

TABLE 6. Results of multivariable logistic fit for microbiological cure

Variable	*P* value
CI	0.01
Synergistic gentamicin treatment	0.32
Days on gentamicin therapy	0.13
Hemodialysis	0.52
Chills	0.45
WBC count	0.48
Age	0.89

AAC 2009;53: 2014–2019

Daptomycin versus Standard Therapy for Bacteremia and Endocarditis Caused by *Staphylococcus aureus*

Vance G. Fowler, Jr., M.D., M.H.S., Helen W. Boucher, M.D., G. Ralph Corey, M.D., Elias Abrutyn, M.D., Adolf W. Karchmer, M.D., Mark E. Rupp, M.D., Donald P. Levine, M.D., Henry F. Chambers, M.D., Francis P. Tally, M.D., Gloria A. Vigliani, M.D., Christopher H. Cabell, M.D., M.H.S., Arthur Stanley Link, M.D., Ignace DeMeyer, M.D., Scott G. Filler, M.D., Marcus Zervos, M.D., Paul Cook, M.D., Jeffrey Parsonnet, M.D., Jack M. Bernstein, M.D., Connie Savor Price, M.D., Graeme N. Forrest, M.D., Gerd Fätkenheuer, M.D., Marcelo Gareca, M.D., Susan J. Rehm, M.D., Hans Reinhardt Brodt, M.D., Alan Tice, M.D., and Sara E. Cosgrove, M.D., for the *S. aureus* Endocarditis and Bacteremia Study Group

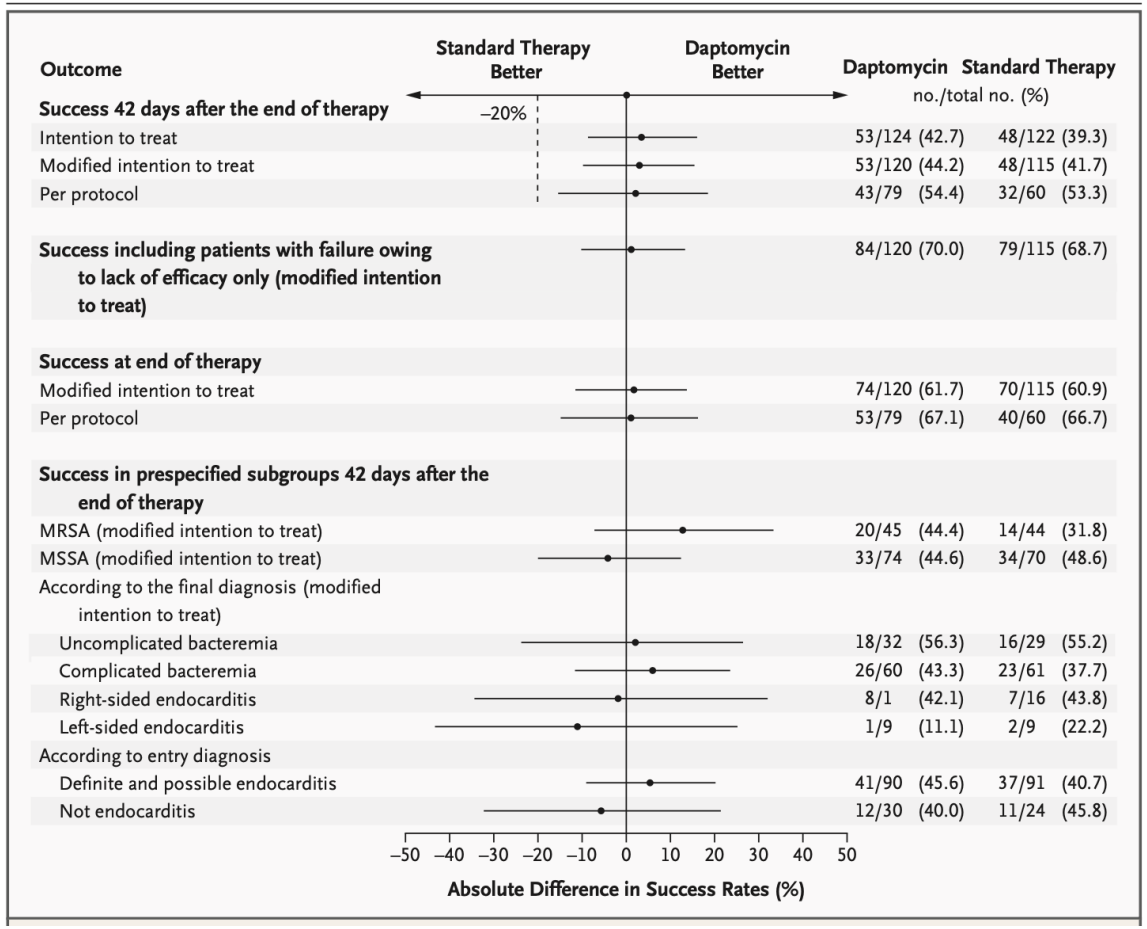
N. Engl. J. Med 2006;355:653-665

Table 3. Reasons for Treatment Failure According to the Adjudication Committee.*

Reason for Failure	Daptomycin (N=120)	Standard Therapy (N=115)	P Value†
	no. (%)		
Overall	67 (55.8)	67 (58.3)	
Microbiologic failure, clinical failure, or both	23 (19.2)	15 (13.0)	0.22
Microbiologic failure‡	19 (15.8)	11 (9.6)	0.17
Clinical failure without microbiologic failure§	4 (3.3)	4 (3.5)	1.00
Adverse event	8 (6.7)	17 (14.8)	0.06
Receipt of nonstudy antibiotics that could have influenced outcome	20 (16.7)¶	16 (13.9)‖	0.59
Death	13 (10.8)	13 (11.3)	1.00
No blood obtained for culture**	9 (7.5)	12 (10.4)	0.50
Patient could not be evaluated (e.g., withdrew consent, left hospital against medical advice)	9 (7.5)	14 (12.2)	0.27

Daptomycin (6 mg/kg daily) is not inferior to standard therapy for S. aureus bacteremia and right-sided endocarditis.

Daptomycin therapy was associated with a higher rate of microbiologic failure than was standard therapy



Ceftobiprole for Treatment of Complicated *Staphylococcus aureus* Bacteremia

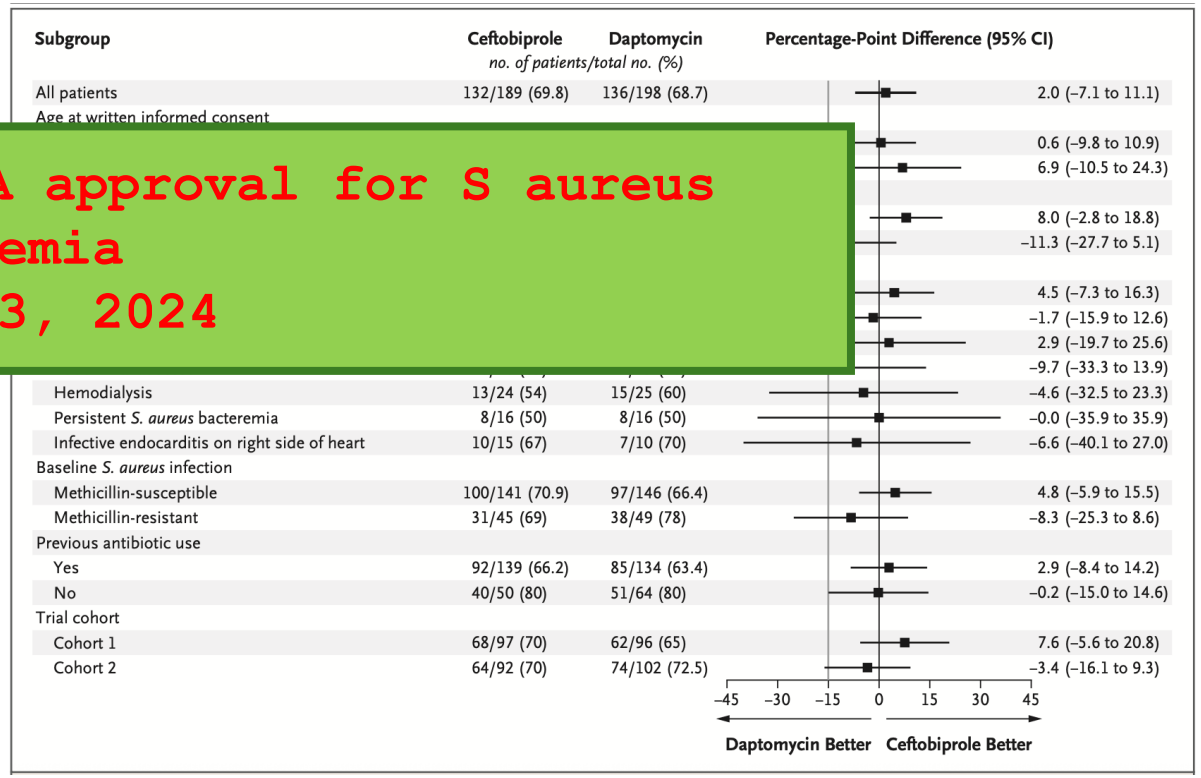
T.L. Holland, S.E. Cosgrove, S.B. Doernberg, T.C. Jenkins, N.A. Turner, H.W. Boucher, O. Pavlov, I. Titov, S. Kosulnykov, B. Atanasov, I. Poromanski, M. Makhviladze, A. Anderzhanova, M.E. Stryjewski, M. Assadi Gehr, M. Engelhardt, K. Hamed, D. Ionescu, M. Jones, M. Saulay, J. Smart, H. Seifert, and V.G. Fowler, Jr., for the ERADICATE Study Group*

N Engl J Med 2023;389:1390-401

Ceftobiprole was non inferior to daptomycin with respect to overall treatment success in patients with complicated S. aureus bacteremia

Methods:
Phase 3, double-blind, non inferiority trial (15%)
>18 y with complicated St. aureus BSI
Randomized 1.1
Ceftobiprol
8h thereaft
Primary ou
70 days afte
clearance, symptom improvement, no new S. aureus bacteremia–related complications, and no receipt of other potentially effective antibiotics)
Results:
189 pts ceftobiprole
198 pts DAP+/- aztreonam

Ceftobiprole received FDA approval for S aureus bacteremia on April 3, 2024



COMBO therapy for MRSA: Why?

- Microbiological failure including persistent and recurrent infection remain a major problem in the management of pts with MRSA bacteriemia and EI
- Limitated efficacy of the current standard antibiotic therapy with Vancomycin or Daptomycin
- Compared to beta-lactam Vancomycin has relatively slow bacterial killing, poor tissue penetration and increase toxicity
- Rapid and effective control of bacteremia for high risk patients
- Daptomycin (6mg/Kg) daily was non inferiori to SOC, but induces resistance strains and subsequent therapeutic failure
- The use of high dose of Daptomycin failures due to persistent or relapsing infections have been reported

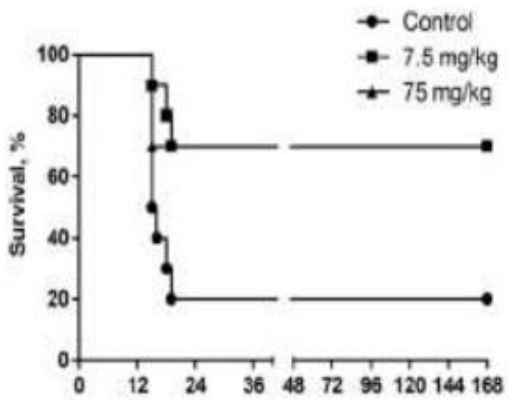
Inagaki K. Clin Infect Dis 2019; 69:2112–8 Liu C.Clin Infect Dis 2011; 52:e18–55 Lodise TP. Clin Infect Dis 2020; 70:1536–45 Davis JS. Clin Infect Dis 2016; 62:173–80 Tong SYC. JAMA 2020; 323:527–37 Thwaites GE. Lancet 2018; 391:668–78 Fowler VG. N Engl J Med 2006; 355:653–65 Gasch O. J Antimicrob Chemother 2014; 69:568–71

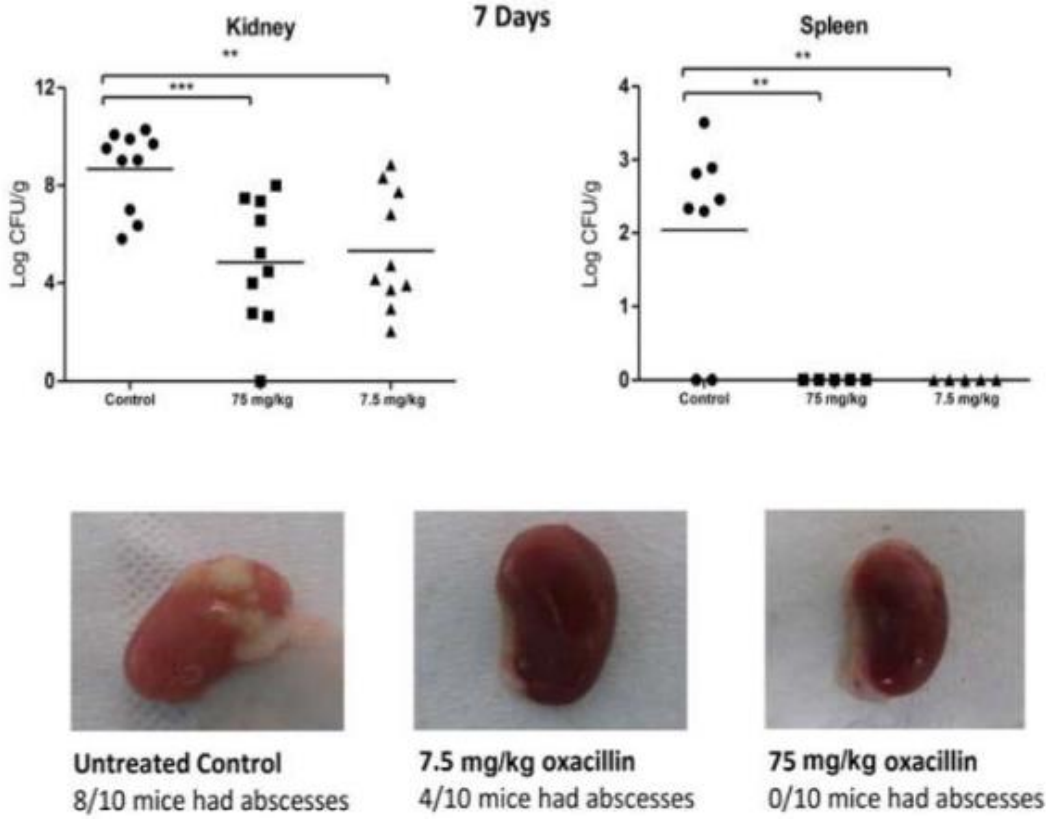
Redeploying β-Lactam Antibiotics as a Novel Antivirulence Strategy for the Treatment of Methicillin-Resistant *Staphylococcus aureus* Infections

Elaine M. Waters,[1,a] Justine K. Rudkin,[3,a] Simone Coughlan,[4] Geremy C. Clair,[7] Joshua N. Adkins,[7] Suzanna Gore,[1] Guoqing Xia,[2] Nikki S. Black,[3] Tim Downing,[4,5] Eoghan O'Neill,[6] Aras Kadioglu,[1,b] and James P. O'Gara[3,b]

AIM: to evaluate if the upregulation of methicillin resistance induced by exposure to oxacillin would downregulate the Agr system and virulence

- **Mice model CA-MRSA**
  - Oxacillin (ASP) started at H9
  - Low & high doses





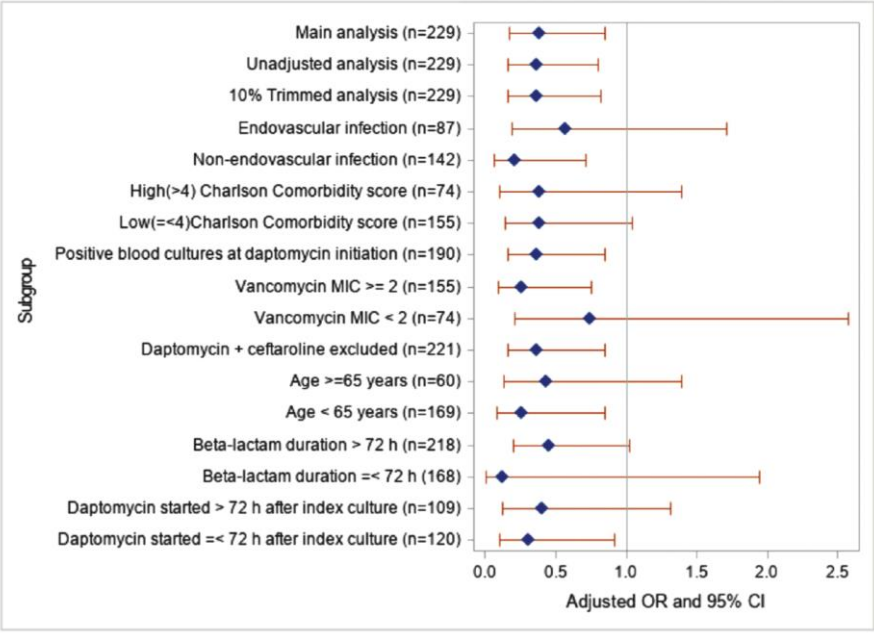
Oxacillin significantly attenuates the virulence of MRSA infections in mouse models of sepsis and pneumonia.

JID 2017;215:80–7

Nafcillin Enhances Innate Immune-Mediated Killing of Methicillin-Resistant *Staphylococcus aureus*

George Sakoulas[1,*], Cheryl Y. Okumura[1,4], Wdee Thienphrapa[1], Joshua Olson[1], Poochit Nonejuie[3], Quang Dam[1], Abhay Dhand[5], Joseph Pogliano[3], Michael R. Yeaman[6], Mary E. Hensler[1], Arnold S. Bayer[6], and Victor Nizet[1,2]

Early Administration of Adjuvant β-Lactam Therapy in Combination with Vancomycin among Patients with Methicillin-Resistant *Staphylococcus aureus* Bloodstream Infection: A Retrospective, Multicenter Analysis



Daptomycin Plus β-Lactam Combination Therapy for Methicillin-resistant *Staphylococcus aureus* Bloodstream Infections: A Retrospective, Comparative Cohort Study

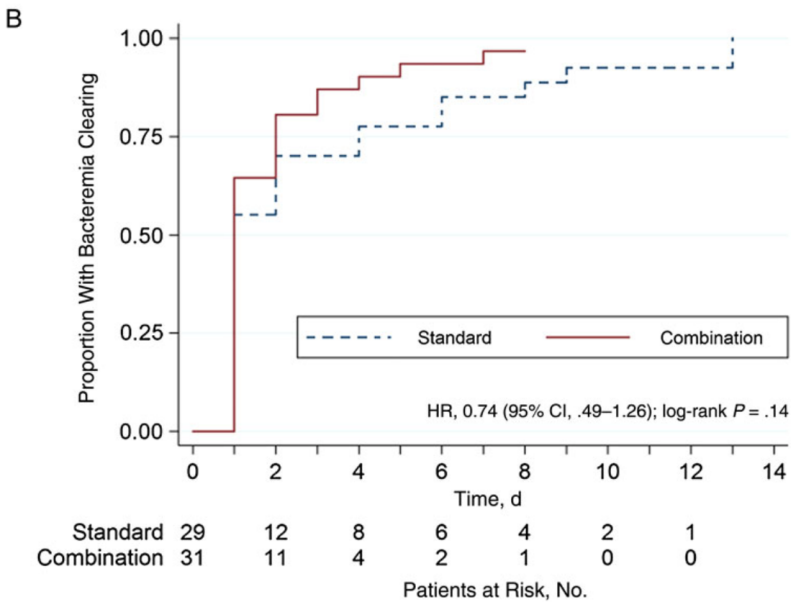
Sarah C. J. Jorgensen,[1] Evan J. Zasowski,[1,2] Trang D. Trinh,[1,3] Abdalhamid M. Lagnf,[1] Sahil Bhatia[1] Noor Sabagha,[1] Jacinda C. Abdul-Mutakabbir,[1] Sara Alosaimy,[1] Ryan P. Mynatt,[4] Susan L. Davis,[1,5] and Michael J. Rybak[1,4,6]

J Mol Med (Berl). 2014 February ; 92(2): 139–149
Pharmacotherapy 2017;37(11):1347–1356
Clinical Infectious Diseases® 2020;71(1):1–10

Combination of Vancomycin and β-Lactam Therapy for Methicillin-Resistant *Staphylococcus aureus* Bacteremia: A Pilot Multicenter Randomized Controlled Trial

Methodology
RCT
>18y
1:1 Vanco + Flucloxacillin 2 g 4 times vs Vanco
Primary outcome: duration of MRSA BSI
Secondary outcomes: (10 days after randomization):

- safety (creatinine of >50%) or hepatotoxicity(>2.5times)
- all-cause 28- and 90-day
- relapsed bacteremia
- metastatic complications
- admission to ICU



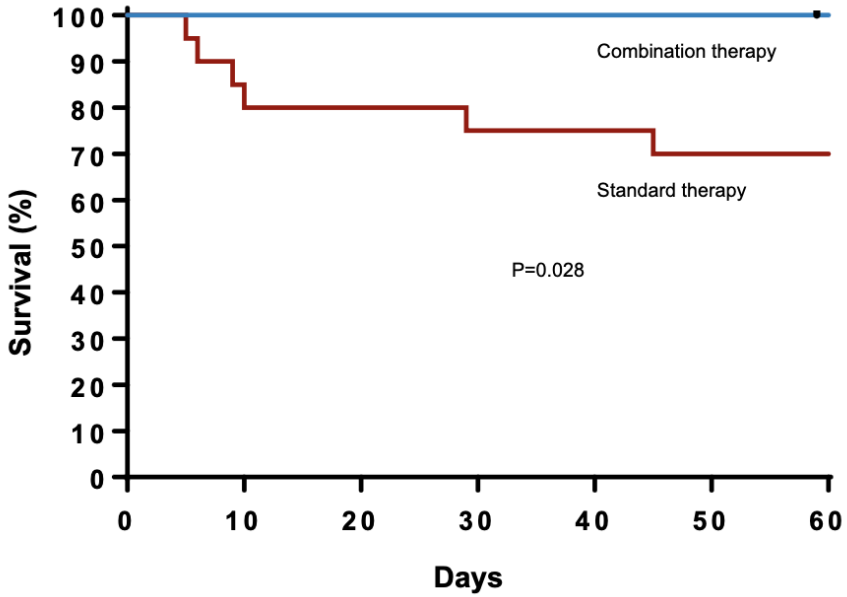
This study provides an encouraging signal that the combination of vancomycin with an antistaphylococcal β-lactam may be useful for the treatment of MRSA bacteremia

Davis JS Clin Infect Dis.2016;62(2):173-180.

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

TABLE 4 Study outcomes

Outcome	Values by treatment type: Combination therapy	Monotherapy	*P* value
Mortality, *n* (%)			
In hospital	0 (0)	6 (26)	0.02
30 day	0 (0)	6 (26)	0.02
90 day	0 (0)	7 (30)	0.03
Bacteremia duration, median (IQR) days	3 (1.5, 5.5)	3 (1, 5.3)	0.56
Length of stay, median (IQR) days	11 (6, 14)	12 (8, 23)	0.24



Higher mortality was seen in patients with endovascular infections and in patients with serum IL-10 concentrations of 5 pg/ml who were treated with monotherapy compared with DAP CPT

Geriak M Antimicrob Agents Chemother 2019; 63(5):e02483 18

AMERICAN SOCIETY FOR MICROBIOLOGY | Antimicrobial Agents and Chemotherapy®

LETTER TO THE EDITOR

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

Andre C. Kalil,[a] Marisa Holubar,[b] Stan Deresinski,[b] Henry F. Chambers[c]

A faulty randomization process, numerous baseline imbalances, premature termination, lack of a prespecified statistical analysis plan, absence of a DSMB, and fragility index of one, strongly suggest that the survival outcome differences were not due to study interventions, but instead due to bias and chance

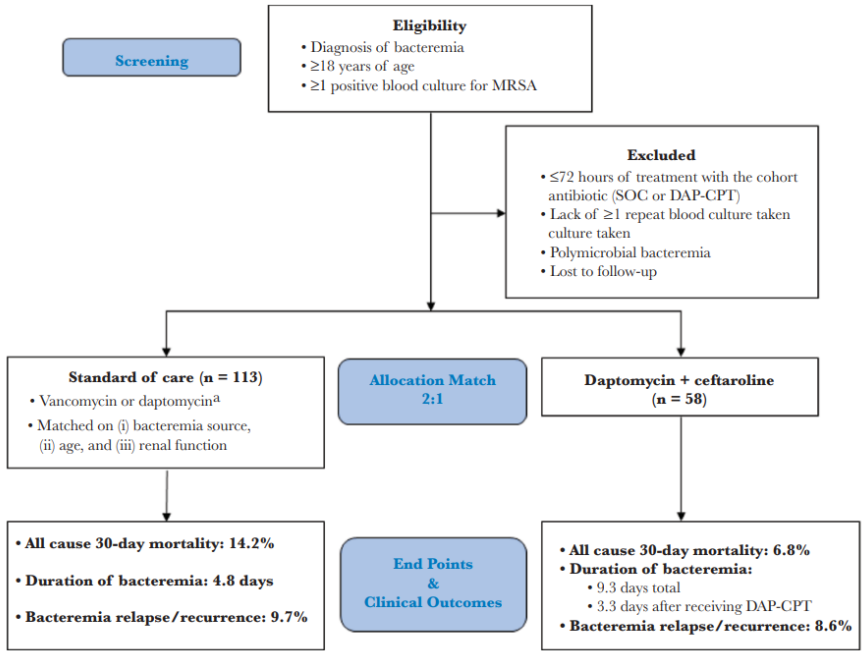
Antimicrobial Agents Chemother 2019; doi:10.1128/AAC.00900-18

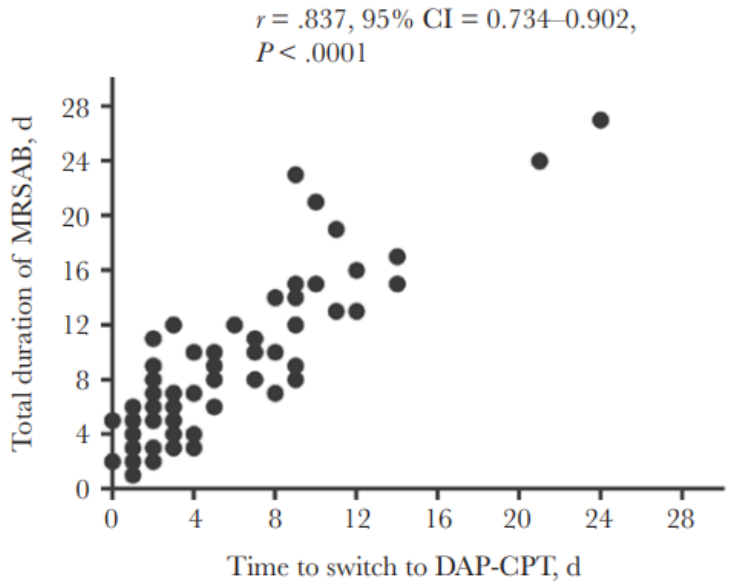
Multicenter Cohort of Patients With Methicillin-Resistant *Staphylococcus aureus* Bacteremia Receiving Daptomycin Plus Ceftaroline Compared With Other MRSA Treatments

Erin K. McCreary,[1,a] Ravina Kullar,[2] Matthew Geriak,[3] Evan J. Zasowski,[4] Khulood Rizvi,[6] Lucas T. Schulz,[1] Krista Ouellette,[3] Logan Vasina,[3] Fadi Haddad,[4] Michael J. Rybak,[5,6] Marcus J. Zervos,[6,7] George Sakoulas,[4,8] and Warren E. Rose[1,9]

Methods:
Retrospective, matched cohort
MRSAB patients
Randomized DAP-CPT for ≥72 hours
matched 2:1
to SOC (infection source, age and renal function)
SOC was: VAN or DAP

Results:
58 DAP-CPT
113 matched SOC
lower mortality in DAP-CPT pts with:
Charlson comorbidity index ≥3, endovascular source
DAP-CPT within 72 hours of index culture.





DAP-CPT treatment is often delayed in MRSAB

Combination therapy may be more beneficial if initiated earlier, particularly in patients at higher risk for mortality

Open Forum Infectious Diseases;2020:7:ofz538

Combination ceftaroline and daptomycin salvage therapy for complicated methicillin-resistant *Staphylococcus aureus* bacteraemia compared with standard of care ☆

Tanner M. Johnson[a,b], Kyle C. Molina[a,b], Matthew A. Miller[a,b], Tyree H. Kiser[a,b], Misha Huang[c,d], Scott W. Mueller[a,b,*]

International Journal of Antimicrobial Agents 57 (2021) 106310

Methods:
Retrospective cohort study included patients with complicated MRSA-BSI
AIM:
Compare:
DAP+CPT vs
SoC: VAN or DAP ± genta or rifa
Primary outcome:
clinical failure (defined as a composite of MRSA-related mortality and recurrent infection at 60d)
Results
60 pts DAP+CPT (n = 30) or SoC (n = 30).
DAP+CPT lower incidence of clinical failure (p=0.052)
At multivariable analysis (correct for IM, CI, and source control) associated DAP+CPT with 77% lower odds of clinical failure (OR 0.23 95%CI 0.06-0.89)

Table 3
Effectiveness outcomes.

Outcome	SoC (control) (n = 30)	DAP+CPT (n =30)	*P*-Value
Clinical failure	13 (43)	6 (20)	0.052
MRSA-related death within 60 days	4 (13)	6 (20)	0.49
Recurrence within 60 days	9 (30)	0	<0.01
All-cause death within 90 days	7 (23)	8 (27)	0.77
Total duration of bacteraemia (days)	5 (4–8)	9 (7–11)	0.01
Time to blood culture clearance on final antibiotic regimen (days)	5 (3–6)	4 (2–5)	0.08
Time to defervescence (h)	102 (27–350)	121 (48–221)	0.93
Time to WBC normalisation (days)	6 (4–18)	13 (10–16)	0.14
60-day hospital-free days	37 (0–46)	34 (2–38)	0.37

SoC, standard of care; DAP, daptomycin; CPT, ceftaroline; MRSA, methicillin-resistant *Staphylococcus aureus*; WBC, white blood cell.
NOTE: All values are presented as n (%) or median (interquartile range). Percentages are of patients for whom data were available.

Table 4
Safety outcomes.

Outcome	SoC (control) (n = 30)	DAP+CPT (n = 30)	*P*-Value
Clostridiodes difficile infection	2 (6.7)	3 (10)	0.99
Neutropenia	0	0	–
Thrombocytopenia	4 (13)	5 (17)	0.99
Mild (100–150 × 10^9 L)	1 (3.3)	1 (3.3)	
Moderate (50–100 × 10^9 L)	1 (3.3)	3 (10)	
Severe (<50 × 10^9 L)	2 (6.7)	1 (3.3)	
CPK elevation	0	3 (10)	0.24
Myopathy	0	2 (6.7)	
Eosinophilic pneumonitis	0	1 (3.3)	0.99
Acute kidney injury	9 (30)	6 (20)	0.37
New dialysis required	0	3 (10)	0.24
Ongoing need after discharge	0	1 (3.3)	
Liver function test increase ≥3× baseline	4 (13)	8 (27)	0.20

SoC, standard of care; DAP, daptomycin; CPT, ceftaroline; CPK, creatine phosphokinase.
NOTE: All values are presented as n (%). Percentages are of patients for whom data were available.

In patients with complicated MRSA-BSI with delayed clearance, DAP+CPT treatment was significantly associated with decreased clinical failure after adjustment for baseline differences.

Daptomycin Plus β-Lactam Combination Therapy for Methicillin-resistant *Staphylococcus aureus* Bloodstream Infections: A Retrospective, Comparative Cohort Study

Sarah C. J. Jorgensen,[1] Evan J. Zasowski,[1,2] Trang D. Trinh,[1,3] Abdalhamid M. Lagnf,[1] Sahil Bhatia[1] Noor Sabagha,[1] Jacinda C. Abdul-Mutakabbir,[1] Sara Alosaimy,[1] Ryan P. Mynatt,[4] Susan L. Davis,[1,5] and Michael J. Rybak[1,4,6]

[1]Anti-Infective Research Laboratory, Eugene Applebaum College of Pharmacy and Health Sciences, Wayne State University, Detroit, Michigan, USA; [2]Department of Clinical Pharmacy, Touro University California College of Pharmacy, Vallejo, California, USA; [3]Department of Clinical Pharmacy, University of California San Francisco School of Pharmacy, San Francisco, California, USA; [4]Department of Pharmacy, Detroit Medical Center, Detroit, Michigan, USA; and [5]Department of Pharmacy, Henry Ford Hospital, Detroit; and [6]School of Medicine, Wayne State University, Detroit, Michigan, USA

DAP+BL pts vs DAP
More AKI (p=0.046)
More CDIs (p=0.08)

Methods:

A retrospective, observational, comparative cohort study between 2008 and 2018.

age > 18 years

positive blood culture for MRSA

DAP+BL pts : DAP started within 5 days of index culture + any BL for 24 hours or more and within 24 hours of initiating DAP

DAP pts: DAP without a BL or less than 24 hours of a BL in the first 5 days of DAP

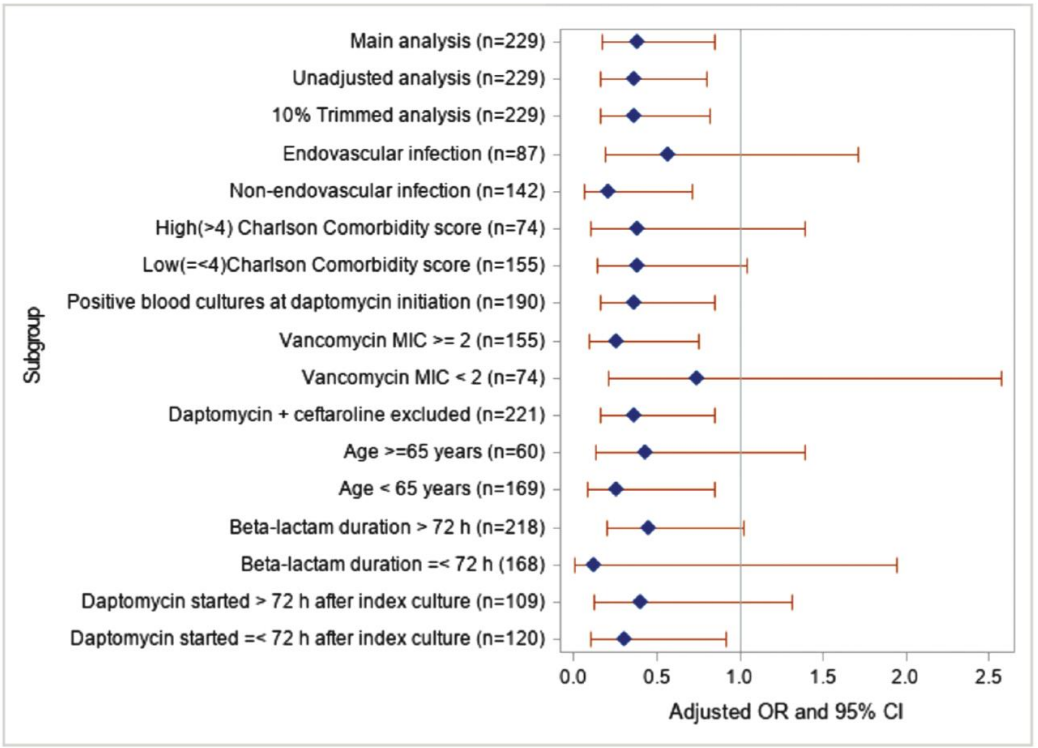
Primary outcome

composite clinical failure (60-day all-cause mortality and/or 60-day recurrence)

Results:

157 pts DAP

72 pts DAP+BL



After careful adjustment for measured confounders, DAP+BL group had a significantly lower odds of clinical failure

Jorgensen SCJ Clin Infect Dis 2020;71:1–10

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Miquel Pujol,[1,a] José-María Miró,[2,a] Evelyn Shaw,[1] Jose-María Aguado,[3] Rafael San-Juan,[3] Mireia Puig-Asensio,[4] Carles Pigrau,[4] Esther Calbo,[5] Miguel Montejo,[6] Regino Rodriguez-Álvarez,[6] María-Jose Garcia-Pais,[7] Vicente Pintado,[8] Rosa Escudero-Sánchez,[8] Joaquín Lopez-Contreras,[9] Laura Morata,[2] Milagros Montero,[10] Marta Andrés,[11] Juan Pasquau,[12] María-del-Mar Arenas,[12] Belén Padilla,[13] Javier Murillas,[14] Alfredo Jover-Sáenz,[15] Luis-Eduardo López-Cortes,[16] Graciano García-Pardo,[17] Oriol Gasch,[18] Sebastian Videla,[19] Pilar Hereu,[19] Cristian Tebé,[20] Natalia Pallarès,[20] Mireia Sanllorente,[19] María-Ángeles Domínguez,[21] Jordi Càmara,[21] Anna Ferrer,[22] Ariadna Padullés,[22] Guillermo Cuervo,[1] and Jordi Carratalà[1,a]; for the MRSA Bacteremia (BACSARM) Trial Investigators

Methods:

RCT (1:1), multicenter, phase 3, superiority, open-label and parallel-group clinical trial

Patients aged ≥18 years with MRSA bacteremia

Intervention:

Dapto 10mg/kg+Fosfo 2 grx6 vs Dapto 10mg/kg

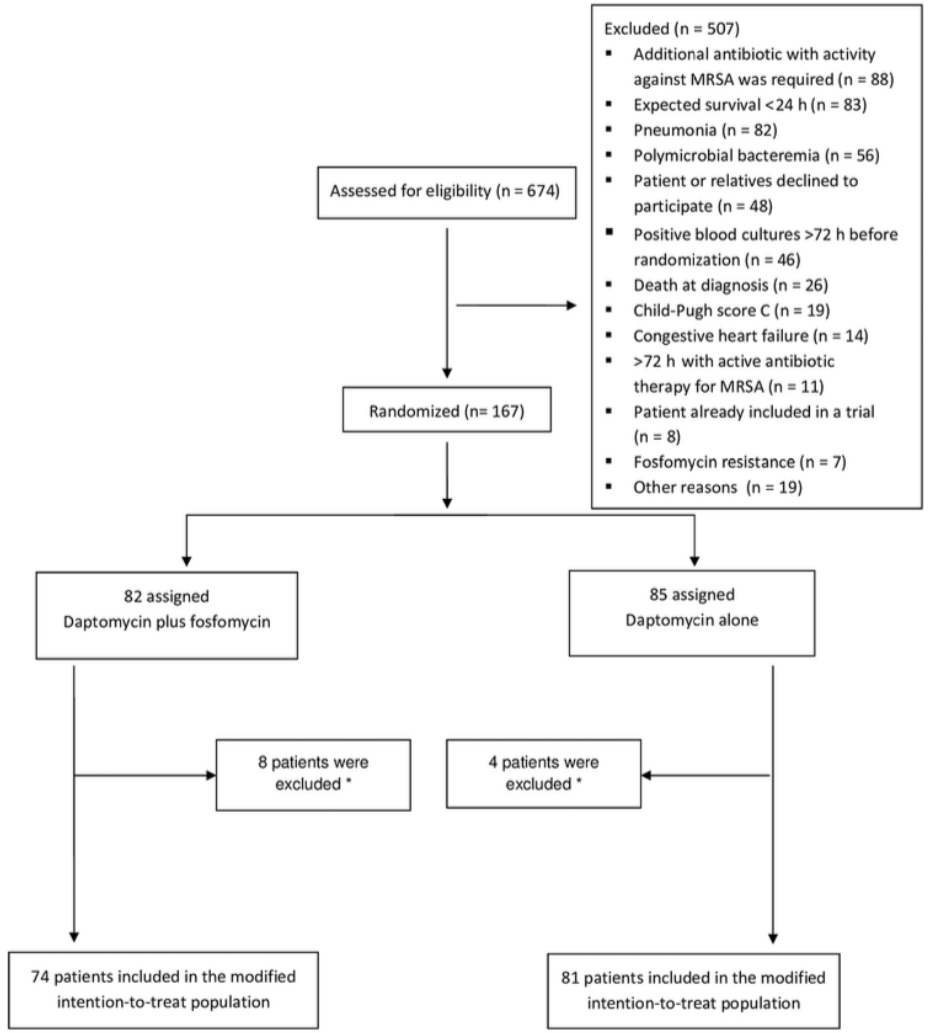
Targeted duration of therapy was 10–14 days or 28–42 days for uncomplicated and complicated bacteremia

Primary endpoint

treatment success at TOC (6 weeks after EOT)

Secondary endpoints:

MRSA bacteremia at day 3, day 7, and/or at TOC; microbiological failure; complicated bacteremia; AEs leading to treatment discontinuation, and mortality due to any cause at day 7 and at TOC



CID 2021:72; 1517-1524

Daptomycin Plus Fosfomycin Versus Daptomycin Alone for Methicillin-resistant *Staphylococcus aureus* Bacteremia and Endocarditis: A Randomized Clinical Trial

Miquel Pujol,[1,a] José-María Miró,[2,a] Evelyn Shaw,[1] Jose-María Aguado,[3] Rafael San-Juan,[3] Mireia Puig-Asensio,[4] Carles Pigrau,[4] Esther Calbo,[5] Miguel Montejo,[6] Regino Rodriguez-Álvarez,[6] María-Jose Garcia-Pais,[7] Vicente Pintado,[8] Rosa Escudero-Sánchez,[8] Joaquín Lopez-Contreras,[9] Laura Morata,[2] Milagros Montero,[10] Marta Andrés,[11] Juan Pasquau,[12] María-del-Mar Arenas,[12] Belén Padilla,[13] Javier Murillas,[14] Alfredo Jover-Sáenz,[15] Luis-Eduardo López-Cortes,[16] Graciano García-Pardo,[17] Oriol Gasch,[18] Sebastian Videla,[19] Pilar Hereu,[19] Cristian Tebé,[20] Natalia Pallarès,[20] Mireia Sanllorente,[19] María-Ángeles Domínguez,[21] Jordi Càmara,[21] Anna Ferrer,[22] Ariadna Padullés,[22] Guillermo Cuervo,[1] and Jordi Carratalà[1,a]; for the MRSA Bacteremia (BACSARM) Trial Investigators

Table 3. Reasons for Treatment Failure at Test of Cure

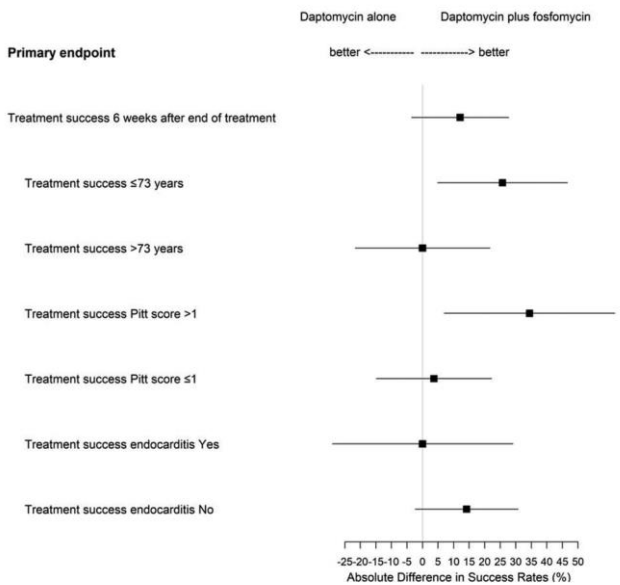
Reason for Treatment Failure	Daptomycin Plus Fosfomycin, No. (%) of Patients (n = 74)	Daptomycin Alone, No. (%) of Patients (n = 81)	Proportion Difference (95% CI)	*P* Value[a]
Treatment failure[b]	34 (45.9)	47 (58.0)	−12.1 (−27.7 to 3.6)	.133
Mortality at TOC	18 (24.3)	22 (27.1)	−2.8 (−16.6 to 10.9)	.687
Clinical failure[c]	0 (0.0)	3 (3.7)	−3.7 (−7.8 to .4)	.247[d]
Microbiological failure	0 (0.0)	9 (11.1)	−11.1 (−18.0 to −4.3)	.003[d]
Any AE leading to treatment discontinuation	13 (17.6)	4 (4.9)	12.6 (2.8–22.5)	.012
Additional antimicrobial therapy administered before TOC[e]	9 (12.1)	19 (23.4)	−11.3 (−23.2 to .6)	.068
Lack of blood cultures at TOC	8 (10.8)	4 (4.9)	5.9 (−2.6 to 14.4)	.172
Loss to follow-up	1 (1.3)	3 (3.7)	−2.4 (−7.2 to 2.5)	.622[d]

Table 2. Primary and Secondary Outcomes

Outcome	Daptomycin Plus Fosfomycin, No. of Patients/Total (%)	Daptomycin Alone, No. of Patients/Total (%)	Relative Risk (95% CI)
Primary endpoint			
Treatment success at TOC	40/74 (54.1)	34/81 (42.0)	1.29 (.93–1.8)
Secondary endpoints			
Positive blood cultures at day 3	2/74 (2.7)	15/81 (18.5)	0.15 (.04–.63)
Positive blood cultures at day 7	0/74 (0.0)	5/81 (6.2)	−6.2 (−11.4 to −.9)[a]
Positive blood cultures at TOC	0/74 (0.0)	4/81 (4.9)	−4.9 (−9.7 to −.2)[a]
Microbiological failure at TOC	0/74 (0.0)	9/81 (11.1)	−11.1 (−18.0 to −4.3)[a]
No. of episodes of complicated bacteremia at TOC	12/74 (16.2)	26/81 (32.1)	0.51 (.28–.94)
Any AE leading to treatment discontinuation	13/74 (17.6)	4/81 (4.9)	3.56 (1.21–10.44)
Overall mortality at day 7	3/74 (4.1)	6/81 (7.4)	0.55 (.14–2.12)
Overall mortality at TOC	18/74 (24.3)	22/81 (27.2)	0.9 (.53–1.54)

Abbreviations: AE, adverse event; CI, confidence interval; TOC, test of cure.

[a]Proportion difference, as it was not possible to estimate the relative risk.



Daptomycin plus fosfomycin provided a 12% higher rate of treatment success than daptomycin alone (not statistical significance).

COMBO:

Higher AE rate (17,6% vs 4,9% p= 0.018)

Higher cure rate (Pitt score >1) (57,1% vs 22,7% p=0.023)

Lower rate of complicated BSI (16,2% vs 32,1% p=0.022)

Lower 6w microbiological failure (0% vs 11.1% p=0.003)

More effective in younger patients

CID 2021:72; 1517-1524

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

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

Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD; Matthew A. Roberts, PhD; Alan Cass, MBBS, PhD; David L. Paterson, MBBS, PhD; Hong Foo, MBBS; Mical Paul, MD; Stephen D. Guy, MBBS; Adrian R. Tramontana, MBBS; Genevieve B. Walls, MBChB; Stephen McBride, MBChB; Narin Bak, MBBS, MPH; Niladri Ghosh, MBBS; Benjamin A. Rogers, MBBS, PhD; Anna P. Ralph, MBBS, PhD; Jane Davies, MBBS, PhD; Patricia E. Ferguson, MBBS, PhD; Ravindra Dotel, MBBS; Genevieve L. McKew, MBBS; Timothy J. Gray, MBBS(Hons); Natasha E. Holmes, MBBS(Hons), PhD; Simon Smith, MBChB; Morgyn S. Warner, MD, PhD; Shirin Kalimuddin, MBBS, MPH; Barnaby E. Young, MBBS; Naomi Runnegar, MBBS; David N. Andresen, MBBS; Nicholas A. Anagnostou, MBBS; Sandra A. Johnson, BSc, MPH; Mark D. Chatfield, MSc; Allen C. Cheng, MBBS, PhD; Vance G. Fowler Jr, MD, MHS; Benjamin P. Howden, MBBS, PhD; Niamh Meagher, MBiostat; David J. Price, PhD; Sebastiaan J. van Hal, MBChB, PhD; Matthew V. N. O'Sullivan, MBBS, PhD; Joshua S. Davis, MBBS, PhD; for the Australasian Society for Infectious Diseases Clinical Research Network

Methods:

RCT powered for superiority
positive blood culture for MRSA
randomized within 72 hours from index culture
>18 years
LOS at least 7 days
Randomized 1:1 SOC (dapto or vanco) vs (dapto or vanco + beta-lactam)

Primary outcome:

composite at 90 days after randomization
1) all-cause mortality
2) persistent bacteremia at study day 5
3) microbiological relapse
4) microbiological treatment failure

Results:

174 pts combo 178 pts mono

Table 3. Primary and Secondary Outcomes

Outcomes	No./Total No. (%)		Risk Difference, % (95% CI)	*P* Value
	Combination Therapy	Standard Therapy		
Primary Outcome[a,b]				
Primary analysis population	59/170 (35)	68/175 (39)	−4.2 (−14.3 to 6.0)	.42
Per protocol	47/144 (33)	68/175 (39)	−6.2 (−16.7 to 4.3)	.25
Secondary Outcomes[c]				
All-cause mortality[d]				
Day 14	13/170 (8)	13/174 (7)	0.2 (−5.4 to 5.8)	.95
Day 42	25/170 (15)	19/174 (11)	3.8 (−3.3 to 10.8)	.29
Day 90	35/170 (21)	28/174 (16)	4.5 (−3.7 to 12.7)	.28
Persistent bacteremia[e]				
Day 2	50/167 (30)	61/173 (35)	−5.3 (−15.3 to 4.6)	.29
Day 5	19/166 (11)	35/172 (20)	−8.9 (−16.6 to −1.2)	.02
Microbiological relapse[a]	14/169 (8)	18/175 (10)	−2.0 (−8.1 to 4.1)	.52
Microbiological treatment failure[a]	16/170 (9)	17/175 (10)	−0.3 (−6.5 to 5.9)	.92
Acute kidney injury[f]	34/145 (23)	9/145 (6)	17.2 (9.3 to 25.2)	<.001
Duration of intravenous antibiotics, mean (SD), d	29.3 (19.5)	28.1 (17.4)		.72

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

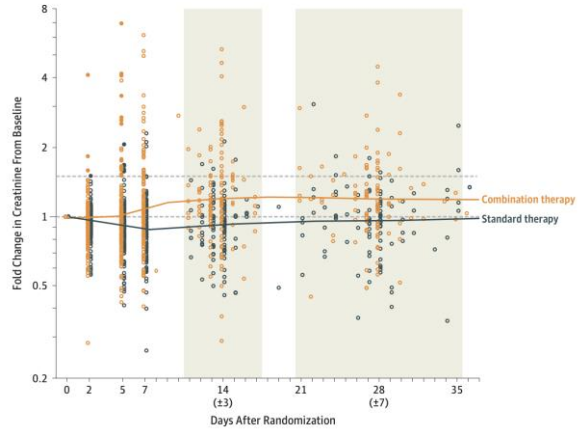
Steven Y. C. Tong, MBBS, PhD; David C. Lye, MBBS; Dafna Yahav, MD; Archana Sud, MD; J. Owen Robinson, MD; Jane Nelson, BN; Sophia Archuleta, MD; Matthew A. Roberts, PhD; Alan Cass, MBBS, PhD; David L. Paterson, MBBS, PhD; Hong Foo, MBBS; Mical Paul, MD; Stephen D. Guy, MBBS; Adrian R. Tramontana, MBBS; Genevieve B. Walls, MBChB; Stephen McBride, MBChB; Narin Bak, MBBS, MPH; Niladri Ghosh, MBBS; Benjamin A. Rogers, MBBS, PhD; Anna P. Ralph, MBBS, PhD; Jane Davies, MBBS, PhD; Patricia E. Ferguson, MBBS, PhD; Ravindra Dotel, MBBS; Genevieve L. McKew, MBBS; Timothy J. Gray, MBBS(Hons); Natasha E. Holmes, MBBS(Hons), PhD; Simon Smith, MBChB; Morgyn S. Warner, MD, PhD; Shirin Kalimuddin, MBBS, MPH; Barnaby E. Young, MBBS; Naomi Runnegar, MBBS; David N. Andresen, MBBS; Nicholas A. Anagnostou, MBBS; Sandra A. Johnson, BSc, MPH; Mark D. Chatfield, MSc; Allen C. Cheng, MBBS, PhD; Vance G. Fowler Jr, MD, MHS; Benjamin P. Howden, MBBS, PhD; Niamh Meagher, MBiostat; David J. Price, PhD; Sebastiaan J. van Hal, MBChB, PhD; Matthew V. N. O'Sullivan, MBBS, PhD; Joshua S. Davis, MBBS, PhD; for the Australasian Society for Infectious Diseases Clinical Research Network

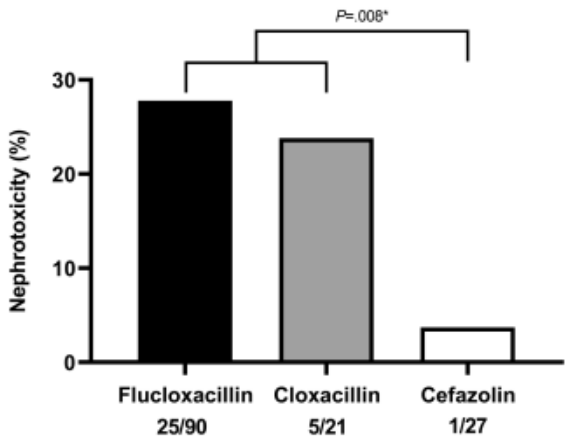
Among patients with MRSA bacteremia, addition of an anti-staphylococcal β-lactam to standard antibiotic therapy with vancomycin or daptomycin did not result in significant improvement in the primary composite end point of mortality, persistent bacteremia, relapse or treatment failure

Table 2. Characteristics of Patients During the Trial in the Primary Analysis Population

Characteristics	Combination Therapy (n = 174)	Standard Therapy (n = 178)
Final diagnosis of infective endocarditis, No. (%)[a]	26 (15)	16 (9)
Received vancomycin, No. (%)[b]	171 (98)	178 (100)
Received daptomycin, No. (%)[b]	7 (4)	6 (3)

Figure 2. Fold Change in Creatinine Levels vs Baseline Measurements





The trial was stopped early because of an excess of AKI in the combination therapy group

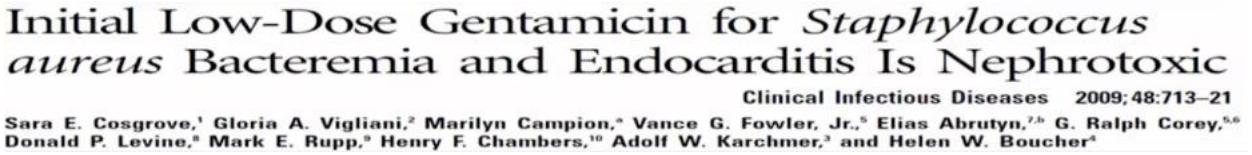
Tong SYC JAMA.2020;323(6):527-537.doi:10.1001/jama.2020.0103
Rose W. CID 2021;73:2353-60

Combination therapy for MSSA and MRSA

- Only 8 randomized clinical trials since 2016
- None demonstrated that combination Abx improved clinical outcomes
  - Rifampin + SAT vs SAT
  - Fosfomycin + SAT vs SAT
  - DAP combined with beta-lactam for MSSA (1 trial)
  - VAN combined with beta-lactam for MRSA (3 trials)
  - DAP+ ceftaroline stopped for mortality
- Combination reduce rates of persistent bacteremia, but it did not improve mortality or treatment success
  - Fosfo+DAP
  - Fosfo+Cloxacillin
  - VAN+ beta-lactam
- Combination therapy is also associated with adverse events

Adjuntive antibiotic for SAB: Guidelines (IDSA)

- Gentamicine: Not Recommended



Initial Low-Dose Gentamicin for *Staphylococcus aureus* Bacteremia and Endocarditis Is Nephrotoxic

Clinical Infectious Diseases 2009; 48:713–21

Sara E. Cosgrove,[1] Gloria A. Vigliani,[2] Marilyn Campion,[a] Vance G. Fowler, Jr.,[5] Elias Abrutyn,[7,b] G. Ralph Corey,[5,6] Donald P. Levine,[8] Mark E. Rupp,[9] Henry F. Chambers,[10] Adolf W. Karchmer,[3] and Helen W. Boucher[4]

- Rifampin: Not Recommended

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

Lancet 2018; 391: 668–78

*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)**

- Antistaphylococcal Penicillin: Not Recommended

JAMA | Original Investigation

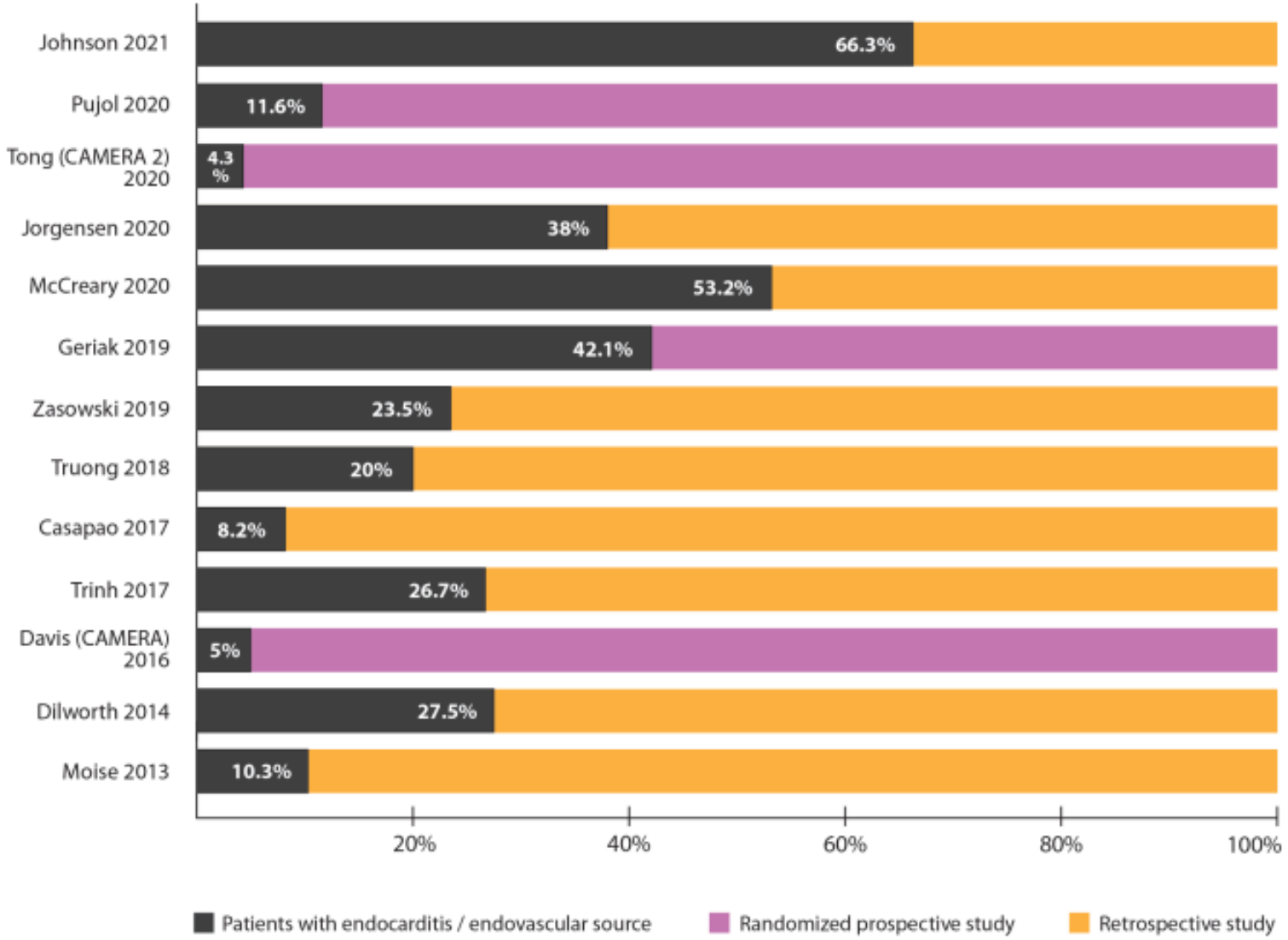
Effect of Vancomycin or Daptomycin With vs Without an Antistaphylococcal β-Lactam on Mortality, Bacteremia, Relapse, or Treatment Failure in Patients With MRSA Bacteremia

A Randomized Clinical Trial

Tong et al, *JAMA* 2020;323(6):527-37

Clinical Infectious Diseases
INVITED ARTICLE
CLINICAL PRACTICE: Ellie J. C. Goldstein, Section Editor

Current Paradigms of Combination Therapy in Methicillin-Resistant *Staphylococcus aureus* (MRSA) Bacteremia: Does it Work, Which Combination, and For Which Patients?



There is significant need to stratify patients based on clinical features and potentially apply new approaches in those high-risk patients

Rose W. CID 2021;73:2353-60

SAB therapy take-home messages

- MSSA: Beta-lactams are better than vancomycin
- MSSA: cefazolin probably safer than nafcillin
  - Caution with IE and other deep seated infections
- MRSA bacteriemia should usually be treated by high-dose daptomycin or vancomycin monotherapy
  - Cheaper
  - Reduced risk of adverse events
  - AMS principles
- Two exceptions: (no data, but many do..)
  - Persistent bacteremia (after 24h max 48h on appropriate treatment)
  - High-risk MRSA bacteremia (including IE and metastatic infections)
  - → high dose daptomycin+beta-lactam (ceftaroline, ceftobiprole) or fosfomycin

Deconstructing the Dogma: Systematic Literature Review and Meta-analysis of Adjunctive Gentamicin and Rifampin in Staphylococcal Prosthetic Valve Endocarditis

Jonathan H. Ryder,[1] Steven Y. C. Tong,[2,3] Jason C. Gallagher,[4] Emily G. McDonald,[5] Irani Thevarajan,[2,3] Todd C. Lee,[5,a] and Nicolás W. Cortés-Penfield[1,a]

Methods:
a systematic review and meta-analysis (4 studies)
AIM:
Evaluate outcomes of staphylococcal PVE treated with adjunctive rifampin, gentamicin, both agents vs monotherapy
Outcomes:
mortality, relapsed infection, length of stay, nephrotoxicity, hepatotoxicity, and drug–drug interactions (DDIs)
Results:
No clinical benefits of either
Genta (OR 0.98;95% CI 0.30-2.46) or
Rifampicin (OR 1,29; 95%CI 0.71-2.33)
Neither gentamicin nor rifampin was associated with reduced infection relapse
Rifampicin was associated with longer hospitalizations (mean, 31.3 vs 42.3 days; P< .001) and AE in 31% of pts

Table 2. Efficacy Outcomes

Study [Reference]	Primary Outcome Definition	Primary Outcome				Relapse/ Recurrence, No. (%)	Hospital LOS, d
		Group 4: BL/Gly Alone, No. (%)	Group 1: Gent + BL/Gly, No. (%)	Group 2: Rif + BL/Gly, No. (%)	Group 3: Rif + Gent + BL/Gly, No. (%)		
Karchmer et al, 1983 [27]	Failure	NR	NR	5/15 (33.3)	2/8 (25)	NR	NR
Karchmer et al, 1983 [24]	Failure	5/10 (50)	3/13 (23.1)	5/15 (33.3)	2/8 (25)	NR	NR
Ramos-Martínez et al, 2018 [26]	1-y all-cause mortality	NR	NR	8/17 (47.1)	38/77 (49.4)	No Gent: 0/17 (0) Gent: 0/77 (0)	NR
Le Bot et al, 2021 [25]	1-y all-cause mortality	NR	25/79 (31.6)	NR	38/101 (37.6)	No Rif: 7/79 (8.9) Rif: 6/101 (5.9)	No Rif: 31.3[a] Rif: 42.3[a]

No study reported repeat surgery outcomes. "Failure" was defined as composite of recurrence and death at up to 3 months. Abbreviations: BL, β-lactam; Gent, gentamicin; Gly, glycopeptide; LOS, length of stay; NR, not reported; Rif, rifampin.

[a]This outcome was significantly different between the 2 groups ($P < .001$ by exact t test).

Open Forum Infectious Diseases 2022,9,ofac583

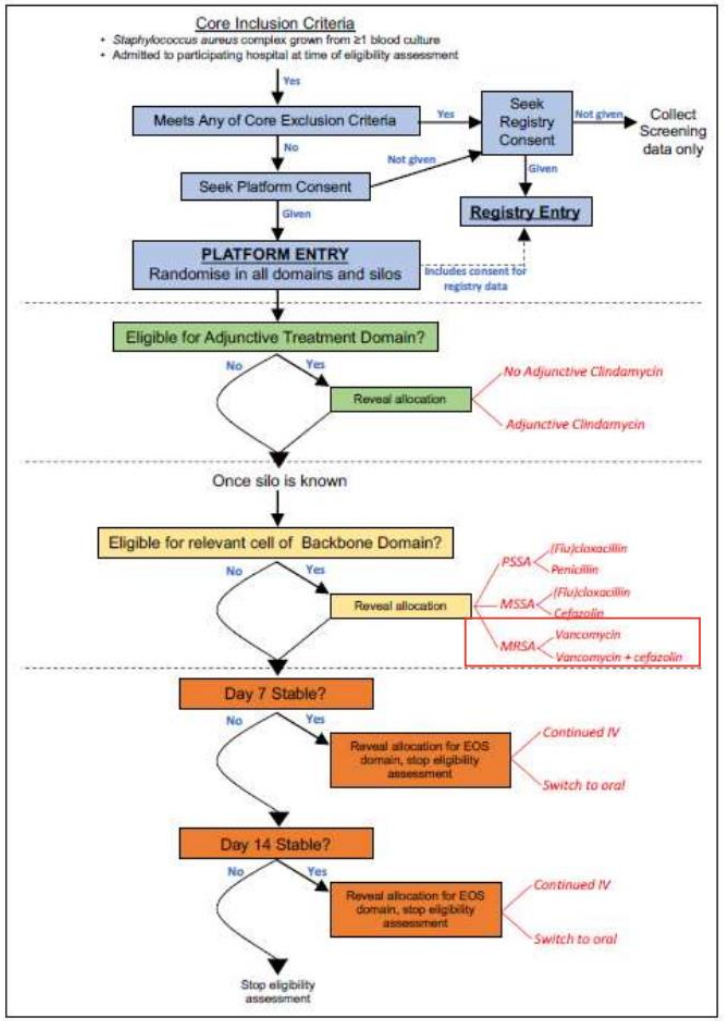
…pending results for MSSA…….

BMJ Open

Efficacy of cloxacillin versus cefazolin for methicillin-susceptible *Staphylococcus aureus* bacteraemia (CloCeBa): study protocol for a randomised, controlled, non-inferiority trial

Charles Burdet,[1,2] Paul Loubet,[1,3] Vincent Le Moing,[4] William Vindrios,[3] Marina Esposito-Farèse,[5,6] Morgane Linard,[2] Tristan Ferry,[7] Laurent Massias,[1,8] Pierre Tattevin,[9] Michel Wolff,[1,10] François Vandenesch,[11] Nathalie Grall,[1,12] Caroline Quintin,[5] France Mentré,[1,2] Xavier Duval,[1,6] François-Xavier Lescure,[1,3] for the CloCeBa study group

SNAP
Staphylococcus aureus
Network Adaptive Platform



Turner *et al. Trials* (2022) 23:407
https://doi.org/10.1186/s13063-022-06370-1

Trials

STUDY PROTOCOL Open Access

Dalbavancin as an option for treatment of *S. aureus* bacteremia (DOTS): study protocol for a phase 2b, multicenter, randomized, open-label clinical trial

Nicholas A. Turner[1], Smitha Zaharoff[2], Heather King[3,4], Scott Evans[5], Toshimitsu Hamasaki[5], Thomas Lodise[6], Varduhi Ghazaryan[7], Tatiana Beresnev[7], Todd Riccobene[8], Rinal Patel[8], Sarah B. Doernberg[9], Urania Rappo[10], Vance G. Fowler Jr[1], Thomas L. Holland[1*] and on behalf of the Antibacterial Resistance Leadership Group (ARLG)

Agenda

- Epidemiology and lethality
- Clinical Characteristics: High Risk and Low Risk
- Persistent *Staphilococcus aureus* Bacteriemia: Definition and Prognosis
- Echo and 18F-FDG PET/CT Scan : when and for which patients
- Antimicrobial Treatment: Guidelines, RCT and real world data
- Early oral switch of antimicrobial therapy
- Special patients: old patients
- Take-home messages

Early oral switch (EOS) for SAB

Background

- Prolonged IV antibiotics (2-6 ws) are the traditional treatmet for SAB
  - Data are predominantly observazional+expert opinion
  - IV best route for instant therapeutic concentration in sick patients: GI dysfunction, impaired level of consciousness etc..may impair administration an absorption in these people

- Prolonged IV treatment can have disadvantages:
  - Adverse drug effects
  - Catheter-associated complications
  - High cost and resource use
  - Inconvenience for patients

Early oral switch (EOS) for SAB

Background

- PK/PD properties of many oral antiobiotics allow drug concetration adeguate for SAB treatment to be achieved once patient stabilised and source control achieved
  - Many PO antibiotics have very good absorption e.g. linezolid (around 100% bioavailability) fluoroquinolones (65-99%), clindamycin (60-90%), rifampicin (>90%), trimethoprim-sulfamethoxazole (70-90%), amoxicillin (74-92%), cefalexin (90%)

- Growing number of clinical studies adding to evidence that early oral switch in SAB is safe and effective:
  - Studies looking at oral switch after a median of 5 days to 17 days of IV therapy
  - Clinical evidence for the safety and effectiveness to early oral switch in SAB treatment is also accruing
  - Comprehensive review of the evidence regarding oral antibiotic use in SAB
  - Ongoing trials of EOS (shorter IV treatment durations) in SAB treatment: RODEO-1

Bupha-Intr 2020, Iversen 2019, Eichenberger 2020, Dagher 2020, Holland 2020, Dagher 2020

Efficacy and safety of an early oral switch in low-risk *Staphylococcus aureus* bloodstream infection (SABATO): an international, open-label, parallel-group, randomised, controlled, non-inferiority trial

Achim J Kaasch, Luis Eduardo López-Cortés, Jesús Rodríguez-Baño, José Miguel Cisneros, M Dolores Navarro, Gerd Fätkenheuer, Norma Jung, Siegbert Rieg, Raphaël Lepeule, Laetitia Coutte, Louis Bernard, Adrien Lemaignen, Katrin Kösters, Colin R MacKenzie, Alex Soriano, Stefan Hagel, Bruno Fantin, Matthieu Lafaurie, Jean-Philippe Talarmin, Aurélien Dinh, Thomas Guimard, David Boutoille, Tobias Welte, Stefan Reuter, Jan Kluytmans, Maria Luisa Martin, Emmanuel Forestier, Hartmut Stocker, Virginie Vitrat, Pierre Tattevin, Anna Rommerskirchen, Marion Noret, Anne Adams, Winfried V Kern, Martin Hellmich, Harald Seifert, for the SABATO study group*

Lancet Infect Dis 2024; 24: 523–34

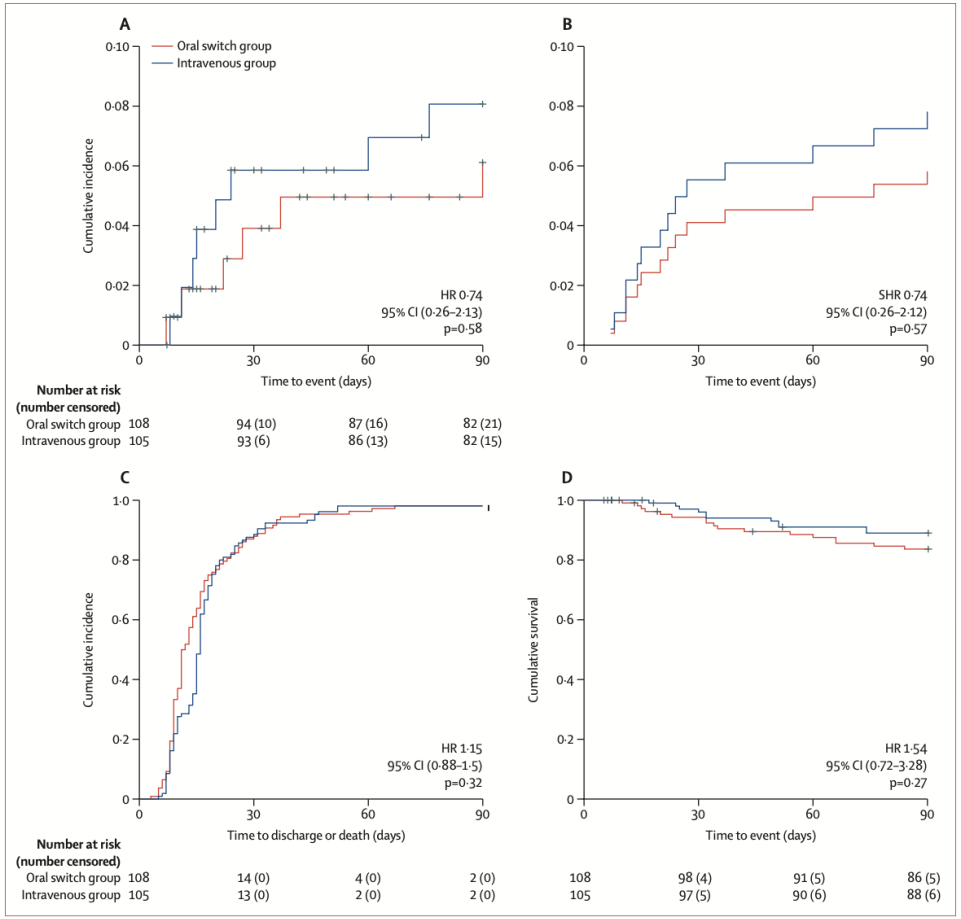
Oral switch antimicrobial therapy was non-inferior to intravenous standard therapy in participants with low-risk S aureus bloodstream infection

Methods:
RCT non inferiority (10%) trial (2013-2019)
Pts >18 with low-risk SAB
Randomized after 5–7 days of IV therapy to oral switch or continue IV therapy for 14 d

Primary outcome:
Composite at 90 days: relapse, deep seated infection, attributable death.

Results:
5063 participants were assessed for eligibility
213 were enrolled in the ITT population
108 pts oral switch group (58% Bactrim, 32% Clinda, 8% Linezolid)
105 to the intravenous group.

Limits:
Only 7.5% MRSA
Anyway previous 5-7 days iv
Small sample only low risk SAB
Limited Pk/PD data on oral therapies



Agenda

- Epidemiology and lethality
- Clinical Characteristics: High Risk and Low Risk
- Persistent *Staphilococcus aureus* Bacteriemia: Definition and Prognosis
- Echo and 18F-FDG PET/CT Scan : when and for which patients
- Antimicrobial Treatment: Guidelines, RCT and real world data
- Early oral switch of antimicrobial therapy
- Special patients: old patients
- Take-home messages

Staphylococcus aureus Bacteremia Among Elderly vs Younger Adult Patients

Comparison of Clinical Features and Mortality

- Prospective cohort of SAB pts:
  - ≥65y 145 pts
  - <60 240 pts

- Significant differences in Elderly vs Younger pts with SAB
  - Afebrile at diagnosis: 4.15 (1.56-11.06)
  - MRSA bacteremia: 1.82 (1.18-2.82)
  - Mortality (total): 2.39 (1.45-3.95)
  - Mortality (attributable) 2.54 (1.26-5.11)

Arch Intern Med 1999;159:1244-1247

Predictors of Mortality with *Staphylococcus aureus* Bacteremia in Elderly Adults

J Am Geriatr Soc 66:1284–1289, 2018.

Matteo Bassetti, MD, PhD, Elda Righi, MD, PhD,* Paola Del Giacomo, MD,† Assunta Sartor, MD,* Filippo Ansaldi, MD,‡ Cecilia Trucchi, MD,‡ Cristiano Alicino, MD,‡ Enrico Maria Trecarichi, MD,† Teresa Spanu, MD,§ Chiara Paganino, MD,‡ Mario Tumbarello, MD,† and Alessia Carnelutti, MD**

Aim:
Indentify risk factors for early and late mortality in pts aged 75 and older with SAB

Methods:
Retrospective observational study (4 y).
All adults consecutively admitted with SAB.

Primary outcome:
Clinical presentation
infection characteristics
clinical outcomes

Results:
337 pts with SAB (35%) ≥75y. In aged pts:
Increase 30d mortality 35.7% vs 20.7% p=0.003.
Unknown focus 52% vs 37% p=0.008
Echocardiography 56.8% vs 71.2% p=0.01
ID consultation 37% vs 60% p<0.001

Table 2. Univariate and Multivariate Analysis of Risk Factors for Mortality at 7 and 30 Days in Individuals Aged 75 and Older

Characteristic	7-Day Mortality, n = 118				30-Day Mortality, n = 115			
	Univariate Analysis			Multivariate Analysis	Univariate Analysis			Multivariate Analysis
	Survived, n = 94	Died, n = 24	P-Value	OR (95% CI) P-Value	Survived, n = 74	Died, n = 41	P-Value	OR (95% CI) P-Value
	n (%)				n (%)			
Baseline disease								
Solid organ transplant recipient	24 (100.0)	0 (0.0)	<.001		0 (0.0)	0 (0.0)		
Solid cancer	22 (23.4)	10 (41.7)	.07		21 (28.4)	10 (24.4)	.64	
Cirrhosis (liver disease qual)	3 (3.2)	6 (25.0)	<.001	8.4 (1.3–75.6) .03	5 (6.8)	4 (9.8)	.57	
Surgery within 30 days	22 (23.4)	6 (25)	.87		23 (31.1)	5 (12.2)	.02	
Echocardiography	56 (59.6)	11 (45.8)	.23		51 (68.9)	16 (39)	.002	
Source of infection								
Unknown	50 (53.2)	12 (50.0)	.78		35 (47.3)	26 (63.4)	.10	
Central venous catheter	12 (12.8)	2 (8.3)	.60		10 (13.5)	4 (9.8)	.58	
Pulmonary	6 (6.4)	2 (8.3)	.73		3 (4.1)	3 (7.3)	.45	
Endocarditis	7 (7.5)	8 (33.3)	<.001		8 (10.8)	7 (17.1)	.34	
Skin soft tissues	5 (5.3)	0 (0.0)	.31		4 (5.4)	1 (2.4)	.52	
Bone	1 (1.1)	0 (0.0)	>.99		1 (1.4)	0 (0.0)	>.99	
Surgical site	5 (5.3)	0 (0.0)	.25		5 (6.8)	0 (0.0)	.11	
Urinary	5 (5.3)	0 (0.0)	.25		5 (6.8)	0 (0.0)	.11	
Other	3 (3.2)	0 (0.0)	.38		3 (4.1)	0 (0.0)	.19	
Methicillin-resistant *Staphylococcus aureus* (susceptibility test)	33 (68.8)	15 (31.3)	.01		24 (51.1)	23 (48.9)	.01	2.4 (1.0–5.7) .04
Septic shock	8 (9.5)	12 (50)	<.001	8.8 (2.7–32) <.001	8 (12.1)	11 (27.5)	.05	2.7 (0.9–8.1)
Intensive care unit admission within 72 hours	2 (2.1)	4 (16.7)	.004		2 (2.7)	4 (9.8)	.10	
Infectious disease consultation (n = 114)	35 (37.6)	6 (25.0)	.25		32 (43.8)	9 (22.0)	.02	0.3 (0.1–0.7) .006
Adequate ab initio	62 (66.0)	10 (41.7)	.03	0.3 (0.1–0.9) .03	50 (67.6)	20 (48.8)	.05	

Only significant results are reported.
OR = odds ratio; CI = confidence interval.

Mortality is significantly higher in elderly with SAB (septic shock, liver cirrhosis and MRSA)
Additional risk factors for mortality included
- inappropriate empiric antibiotic treatment
- no ID consult

Clinical presentation, management and outcomes of *Staph aureus* bacteremia (SAB) in older adults

Dafna Yahav[1,2] · Agata Schlesinger[2,3] · Hila Shaked[1] · Elad Goldberg[2,4] · Mical Paul[2,5] · Jihad Bishara[1,2] · Leonard Leibovici[2,6]

- Retrospective cohort of >1600 pts with SAB:
  - 2/3 ≥65y
  - 1/3 <65y
- Presentation different:
  - More afebrile
  - More leukocytosis and shock
- Management different
  - Lower TEE
  - Lower ID Consult
- Outcome different
  - Higher mortality 47.5% vs 23.2%

Aging Clin Exp Res (2017) 29:127–133

Atypical Presentation of Bacteremia in Older Patients Is a Risk Factor for Death

The American Journal of Medicine, 2019;132,1344-1352

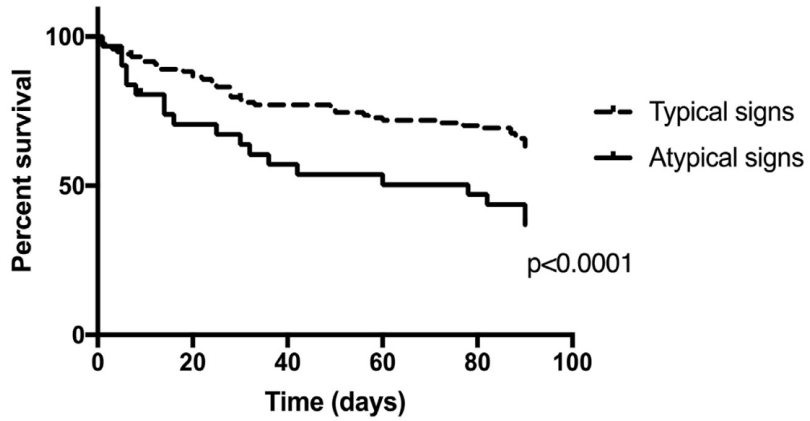
Caroline Hyernard, MD,[a] Alice Breining, MD,[b] Sophie Duc, MD,[a] David Kobeh, MD,[a] Maria Dubos, MD,[a] Renaud Prevel, MD,[a] Charles Cazanave, MD, PhD,[c,d] Mathieu Lambert, MD,[e] Fabrice Bonnet, MD, PhD,[f] Patrick Mercie, MD, PhD,[g] Anne Contis, MD, PhD,[g] Piere Duffau, MD, PhD,[g] Fabrice Camou, MD, PhD,[h] Florent Guerville, MD,[a] Muriel Rainfray, MD, PhD,[a] Claire Roubaud-Baudron, MD, PhD[a,i]

Aim:
evaluate whether atypical presentation (AP) of bacteremia was associated to mortality
factors associated with AP.

Methods:
observational prospective study 2 French hospitals
patients ≥ 75 years with bacteremia.
AP= absence of a temperature ≥38.3˚C or < 36˚C, chills, or hypotension.

Primary outcome:
Mortality at 1 week (D7) and 3 months (D90).

Results:
151 old patients (21.2%) with AP
AP was independently associated with
D7 (OR 4.46, 95% CI 1.04-19.24)
D90 (OR 3.76, 95% CI 1.30-10.92) mortality
Patients with diabetes and SAB have more AP



	Survival, n (%)			
Time	D0	D7	D30	D90
Typical signs	119 (100.0)	112 (94.1)	96 (81.4)	70 (64.8)
Atypical signs	32 (100.0)	27 (84.4)	22 (68.8)	12 (40.0)

Blood culture should be considered for patients who are older, especially with diabetes with acute unexplained clinical manifestations.

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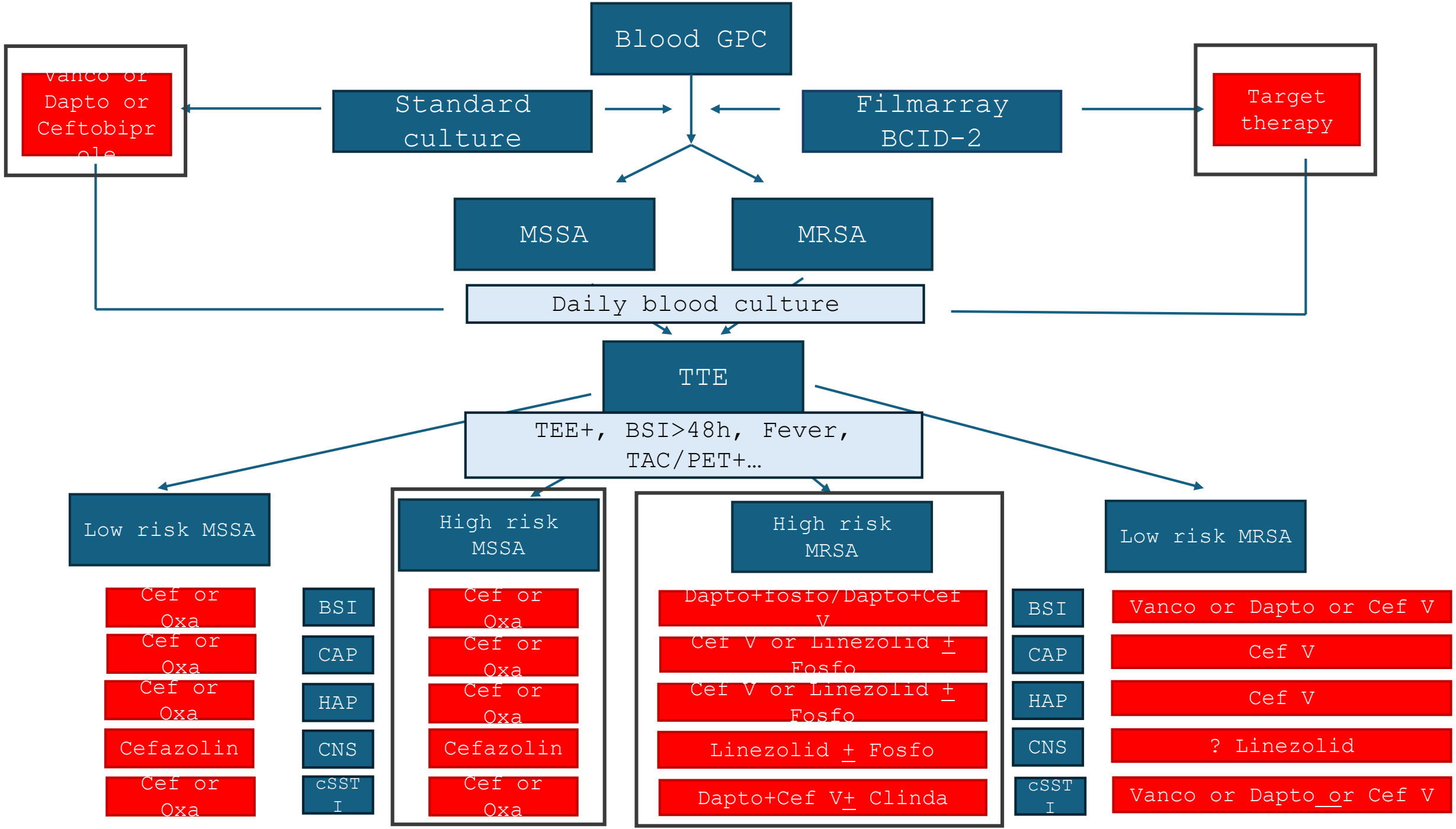
Take-home messages

- The first days of treatment for SAB involve:
    - Appropriate Abx Therapy, Screening Echocardiography, Assessment Metastatic Phenomena, Source Control, ID Consult and Daily blood culture

- MRSA: IDSA guidelines recommend vancomycin, daptomycin or ceftobiprole monoterapy for MRSA bacteremia
- MRSA: Combination therapy (DAP+CEFT or DAP+ FOSFO) may offers some benefits in term of bacteremia clearance, it does not consistently improve mortality outcomes and carries a higher risk of nephrotoxicity (considered case-by-case)
- MRSA: Combination therapy should to mitigate the development of resistance, particular beneficial in the early intensive phase (high inoculum) followed by a monotherapy de-escalation for consolidation phase (clinical trials are needed)

- MSSA: ASP and cefazolin are considered first line agents
- MSSA: for severe infection (IE) combination therapy with DAP+Beta-lactam has shown superior efficacy in experimental models (clinical trials are needed)


Blood GPC
Vanco or Dapto or Ceftobiprole
Standard culture
Filmarray BCID-2
Target therapy
MSSA
MRSA
Daily blood culture
TTE
TEE+, BSI>48h, Fever, TAC/PET+…
Low risk MSSA
High risk MSSA
High risk MRSA
Low risk MRSA
Cef or Oxa
Cef or Oxa
Cef or Oxa
Cefazolin
Cef or Oxa
BSI
CAP
HAP
CNS
cSSTI
Cef or Oxa
Cef or Oxa
Cef or Oxa
Cefazolin
Cef or Oxa
Dapto+fosfo/Dapto+Cef V
Cef V or Linezolid ± Fosfo
Cef V or Linezolid ± Fosfo
Linezolid ± Fosfo
Dapto+Cef V± Clinda
BSI
CAP
HAP
CNS
cSSTI
Vanco or Dapto or Cef V
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? Linezolid
Vanco or Dapto or Cef V


thank you
danke
謝謝
ngiyabonga
рахмат
teşekkür ederim
gracias
спасибо
faafetai lava
Баярлалаа
dank je
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