Bloodstream Infections

Update in Hospital Medicine

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- Grant funding
  - Centers for Disease Control and Prevention
  - Agency for Healthcare Research and Quality
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- Royalties
  - UpToDate for chapters on pneumonia

Outline

- **Gram negative bacteremia**
  - One drug or two?
  - Preferred agents for ESBL
  - Duration of treatment
- **Gram positive bacteremia**
  - What's the best drug for MSSA?
  - What's the best drug for MRSA
  - What do I do if the Vanco MIC is elevated?
- **General**
  - Does my patient need an echo?
  - Should I place a PICC or a midline?
  - Can we treat with orals?

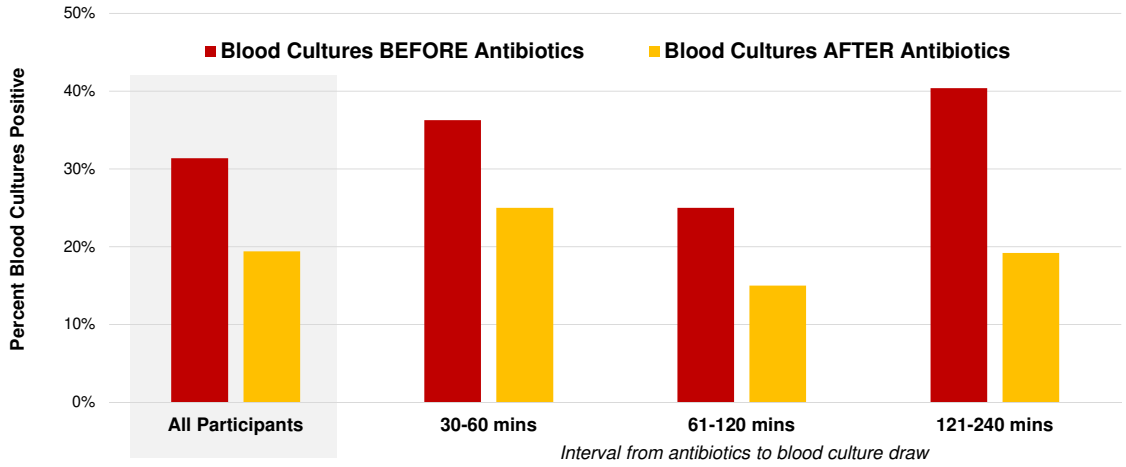
Case Study

- A 64 year old woman is admitted to the hospital with high fever and altered mental status. She has a remote history of cardiac arrest, coronary artery disease, and congestive heart failure with low ejection fraction for which she had an AICD placed 2 months ago. She also had elective cataract surgery two weeks ago. She has a history of recurrent UTIs secondary to ceftriaxone-resistant *E. coli.*
- Your examination is notable for lethargy, anasarca, and tachycardia.
- Vitals: temp 102.3, HR 110, BP 80/60, RR 32, SaO2 88% on ambient air
- You order a CBC/diff, CMP, lactate, UA, procalcitonin, blood cultures, and CXR
- You decide to start empiric antibiotics.

The patient is pretty sick.
Do we really need to get blood cultures before we give antibiotics?

Antibiotics Before Blood Cultures Lower Yield by ~50%

Blood cultures drawn before and 30-120mins after antibiotics in 325 patients with suspected septic shock

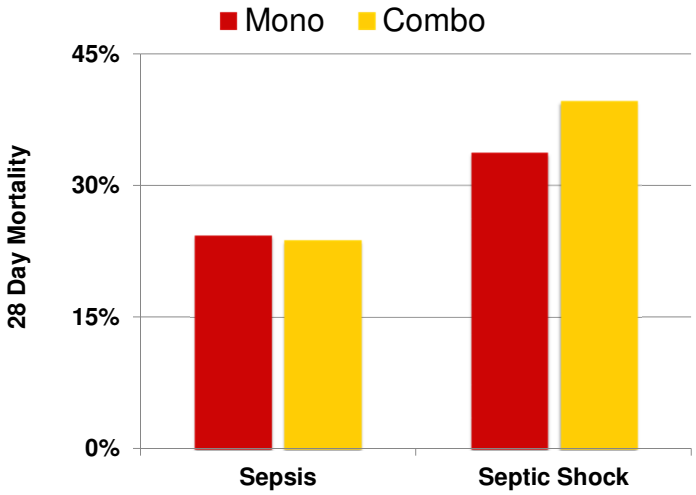


Ann Intern Med 2019; doi:10.7326/M19-1696

Should we start one drug or two to cover Gram negatives?

RCT of Mono vs Combo Rx for Sepsis

600 patients randomized to meropenem alone vs meropenem + moxifloxacin

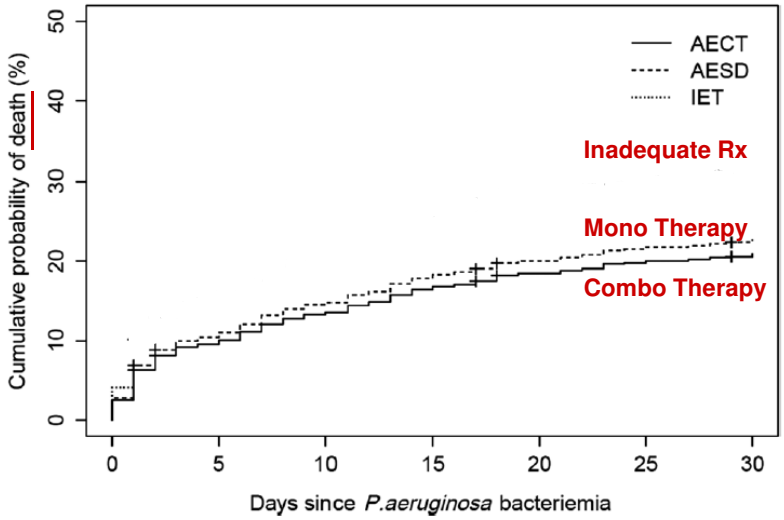


No difference!

Brunkhorst, *JAMA* 2012;307:2390-2399

Mono vs Combo Rx for Pseudomonas Bacteremia

Prospective cohort study of 674 patients with Pseudomonas bacteremia



Active therapy matters more than combo vs mono therapy!

Pena, Clin Infect Dis 2013;57:208-216

Does it matter what drug we use to treat ESBLs so long as the bacteria is "susceptible?"

Pip-Tazo vs Meropenem for ESBL *E. coli* or *Klebsiella sp.*

JAMA | Original Investigation

Effect of Piperacillin-Tazobactam vs Meropenem on 30-Day Mortality for Patients With *E coli* or *Klebsiella pneumoniae* Bloodstream Infection and Ceftriaxone Resistance
A Randomized Clinical Trial

Patrick N. A. Harris, MBBS; Paul A. Tambyah, MD; David C. Lye, MBBS; Yin Mo, MBBS; Tau H. Lee, MBBS; Mesut Yilmaz, MD; Thamer H. Alenazi, MD; Yaseen Arabi, MD; Marco Falcone, MD; Matteo Bassetti, MD, PhD; Elda Righi, MD, PhD; Benjamin A. Rogers, MBBS, PhD; Souha Kanj, MD; Hasan Khaly, MBBS; Jon Iredell, MBBS, PhD; Marc Mendelson, MBBS, PhD; Tom H. Boyles, MD; David Looke, MBBS; Sphiwe Mlyaba, MD, PhD; Genevieve Walls, MB, ChB; Mohammed Al Khamis, MD; Ahmed Zikri, PharmD; Amy Crowe, MBBS; Paul Ingram, MBBS; Nick Daneman, MD; Paul Griffin, MBBS; Eugene Athan, MBBS, MPH, PhD; Penelope Lorenz, RN; Peter Baker, PhD; Leah Roberts, BSc; Scott A. Beatson, PhD; Anton Y. Peleg, MBBS, PhD; Tiffany Harris-Brown, RN, MPH; David L. Paterson, MBBS, PhD; for the MERINO Trial Investigators and the Australasian Society for Infectious Disease Clinical Research Network (ASID-CRN)

IMPORTANCE Extended-spectrum β-lactamases mediate resistance to third-generation cephalosporins (eg, ceftriaxone) in *Escherichia coli* and *Klebsiella pneumoniae*. Significant infections caused by these strains are usually treated with carbapenems, potentially selecting for carbapenem resistance. Piperacillin-tazobactam may be an effective "carbapenem-sparing" option to treat extended-spectrum β-lactamase producers.

OBJECTIVES To determine whether definitive therapy with piperacillin-tazobactam is noninferior to meropenem (a carbapenem) in patients with bloodstream infection caused by ceftriaxone-nonsusceptible *E coli* or *K pneumoniae*.

DESIGN, SETTING, AND PARTICIPANTS Noninferiority, parallel group, randomized clinical trial included hospitalized patients enrolled from 26 sites in 9 countries from February 2014 to July 2017. Adult patients were eligible if they had at least 1 positive blood culture with *E coli* or *Klebsiella* spp testing nonsusceptible to ceftriaxone but susceptible to piperacillin-tazobactam. Of 1646 patients screened, 391 were included in the study.

INTERVENTIONS Patients were randomly assigned 1:1 to intravenous piperacillin-tazobactam, 4.5 g, every 6 hours (n = 188 participants) or meropenem, 1 g, every 8 hours (n = 191 participants) for a minimum of 4 days, up to a maximum of 14 days, with the total duration determined by the treating clinician.

MAIN OUTCOMES AND MEASURES The primary outcome was all-cause mortality at 30 days after randomization. A noninferiority margin of 5% was used.

RESULTS Among 379 patients (mean age, 66.5 years; 47.8% women) who were randomized appropriately, received at least 1 dose of study drug, and were included in the primary analysis population, 378 (99.7%) completed the trial and were assessed for the primary outcome. A total of 23 of 187 patients (12.3%) randomized to piperacillin-tazobactam met the primary outcome of mortality at 30 days compared with 7 of 191 (3.7%) randomized to meropenem (risk difference, 8.6% [1-sided 97.5% CI, −∞ to 14.5%]; $P = .90$ for noninferiority). Effects were consistent in an analysis of the per-protocol population. Nonfatal serious adverse events occurred in 5 of 188 patients (2.7%) in the piperacillin-tazobactam group and 3 of 191 (1.6%) in the meropenem group.

CONCLUSIONS AND RELEVANCE Among patients with *E coli* or *K pneumoniae* bloodstream infection and ceftriaxone resistance, definitive treatment with piperacillin-tazobactam compared with meropenem did not result in a noninferior 30-day mortality. These findings do not support use of piperacillin-tazobactam in this setting.

TRIAL REGISTRATION anzctr.org.au Identifiers: ACTRN12613000532707 and ACTRN12615000403538 and ClinicalTrials.gov Identifier: NCT02176122

JAMA. 2018;320(10):984-994. doi:10.1001/jama.2018.12163
Corrected on June 18, 2018.

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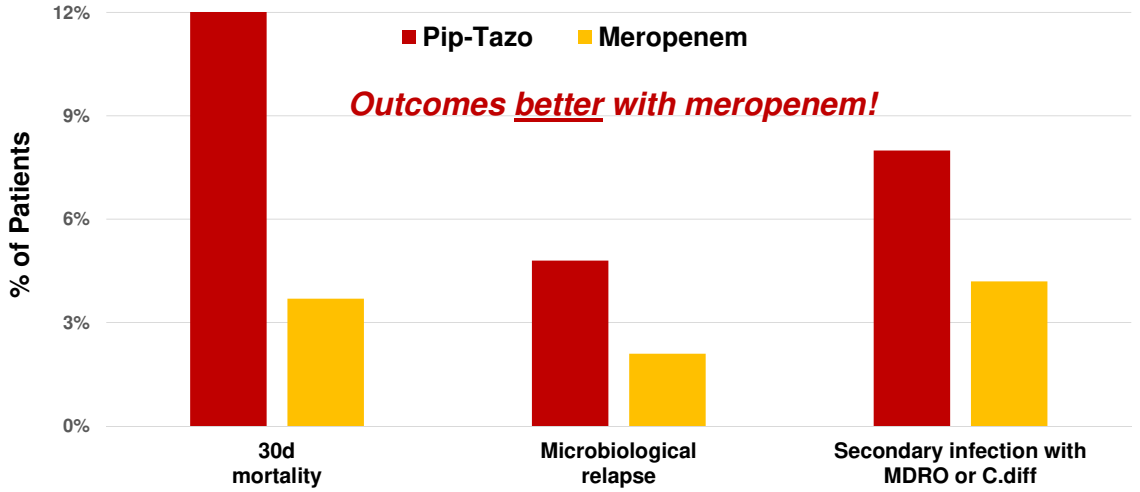
984 jama.com

- 391 patients with ≥1 positive blood culture for *E. coli* or *Klebsiella sp.* resistant to ceftriaxone, susceptible to piperacillin-tazobactam
- Randomized to pip-tazo 4.5g IV q6h vs meropenem 1g IV q8h for 4-14d
- Primary outcome: 30d mortality

Harris, *JAMA* 2018;320:984-994

Pip-Tazo vs Meropenem for ESBL *E. coli* or *Klebsiella sp.*

391 patients with E. coli or Klebsiella sp. bacteremia randomized to pip-tazo vs meropenem



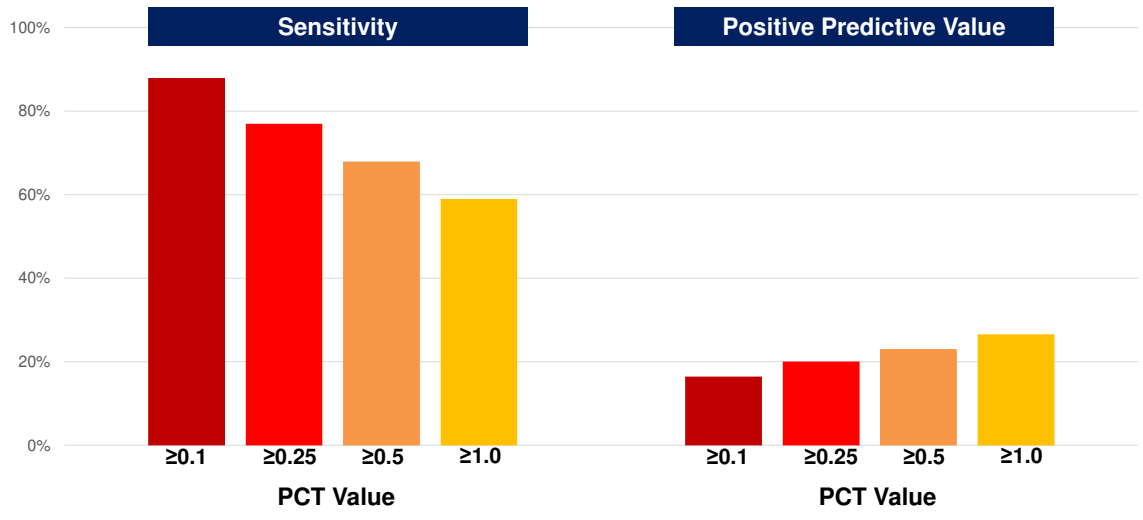
JAMA 2018;320:984-994

Case Study Continued

- You begin empiric therapy with vancomycin and meropenem
- One day later, the patient looks a little better but is still febrile.
- Procalcitonin is 0.18.
- You call the lab to ask if the blood cultures are growing anything?
- The answer: “nothing yet”

Does a low procalcitonin rule out bacteremia?

Sensitivity / PPV of Procalcitonin for Bacteremia

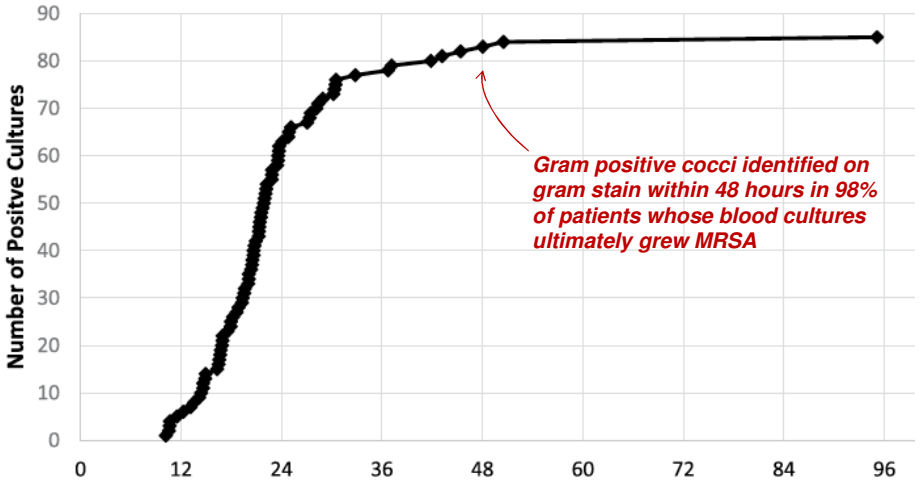


Lawandi, *Crit Care Med* 2023; doi 10.1097/CCM.0000000000005968

How long do I need to wait to be confident the blood cultures won't grow *Staph aureus*?

Blood cultures: Time to positivity

85 patients with MRSA bacteremia, 5 ICUs, Vanderbilt University

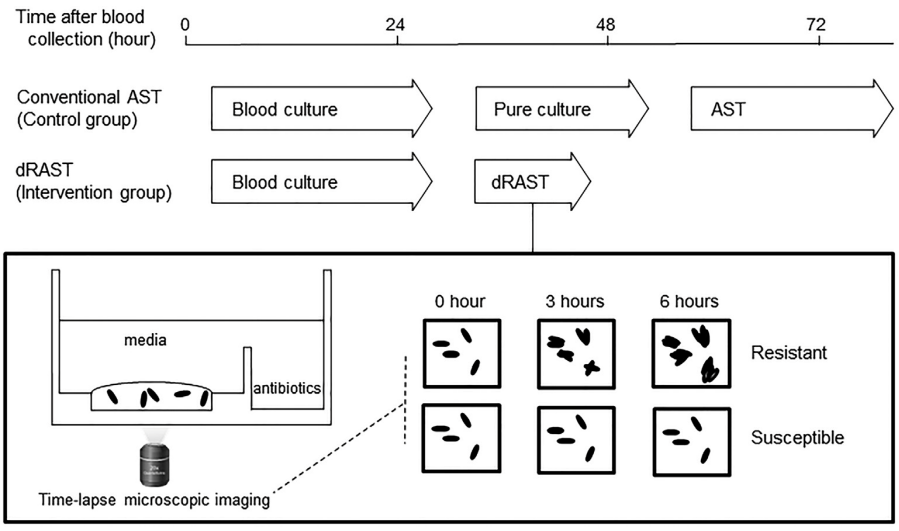


Melling, *Ann Pharmacotherapy* 2020;54:131-137

Do we really need to wait 2-3 days to get susceptibilities?

Isn't there a faster way?

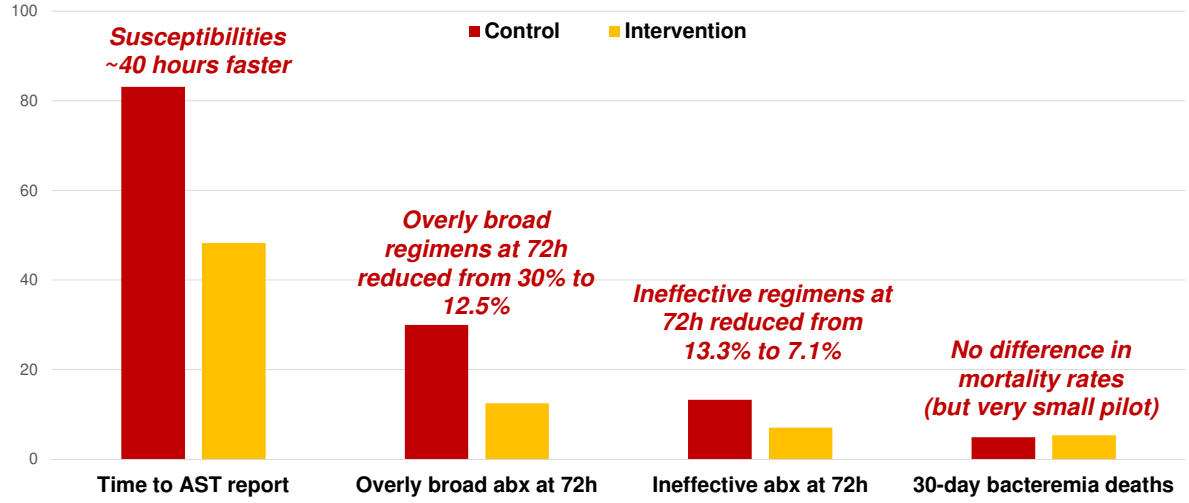
Rapid Antimicrobial Susceptibility Testing



Kim, *Clin Micro Infection* 2021;27:69-75

Rapid Antimicrobial Susceptibility Testing

Pilot randomized trial, 116 pts with heme malignancies and +blood cultures, Seoul National University Hospitals



Kim, *Clin Micro Infection* 2021;27:69-75

Case Study Continued

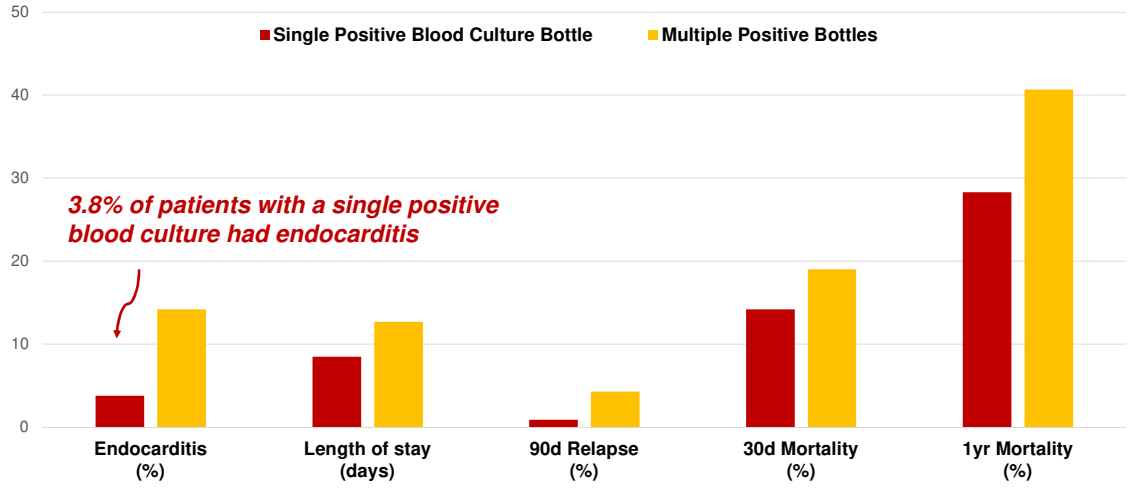
- Just when you were about to give up hope on finding an answer, the lab pages you:
  - "Your patient has one positive blood culture bottle. The Gram stain shows Gram positive cocci in clusters"
- You suspect *Staphylococcus aureus* and arrange a follow-up set of blood cultures to be drawn

What is the significance of a single positive blood culture with *Staph aureus*?

Significance of one blood culture positive for *Staph aureus*

534 patients with Staph aureus bacteremia (22% single positive, 78% multiple positive bottles), 4 Mayo Clinic hospitals

All told, 90% of single positive blood cultures were deemed clinically significant

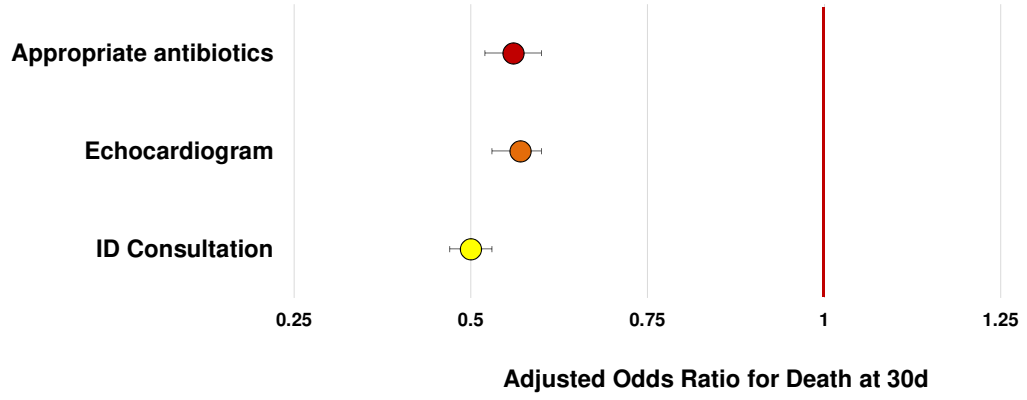


Go, *Open Forum Infect Dis* 2022;ofab642

Should we get an Infectious Disease consult?

Care Processes and Mortality in *Staph aureus* Bacteremia

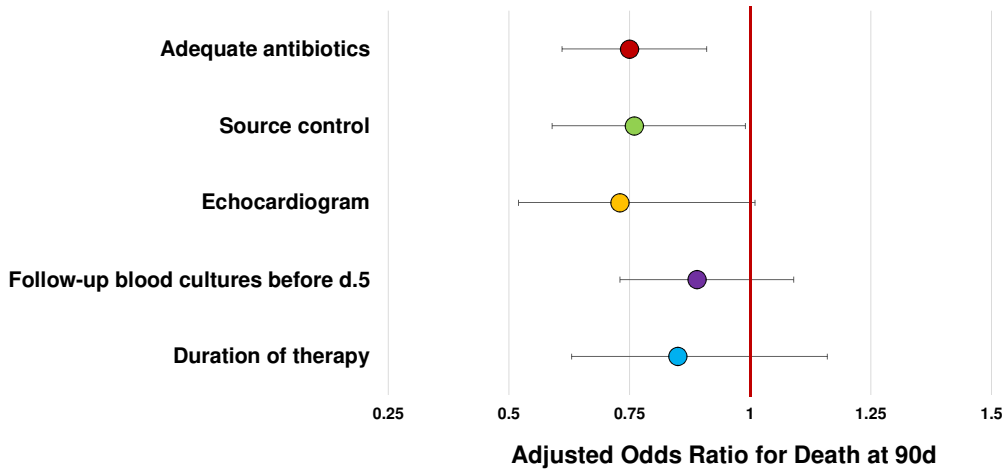
36,868 episodes of Staph aureus bacteremia, 124 VA hospitals, 2003-2014



Goto, *JAMA Internal Medicine* 2017;177:1489-1497

Care Processes and Mortality in *Staph aureus* Bacteremia

1,784 episodes of Staph aureus bacteremia, multinational cohort, 2013-2015



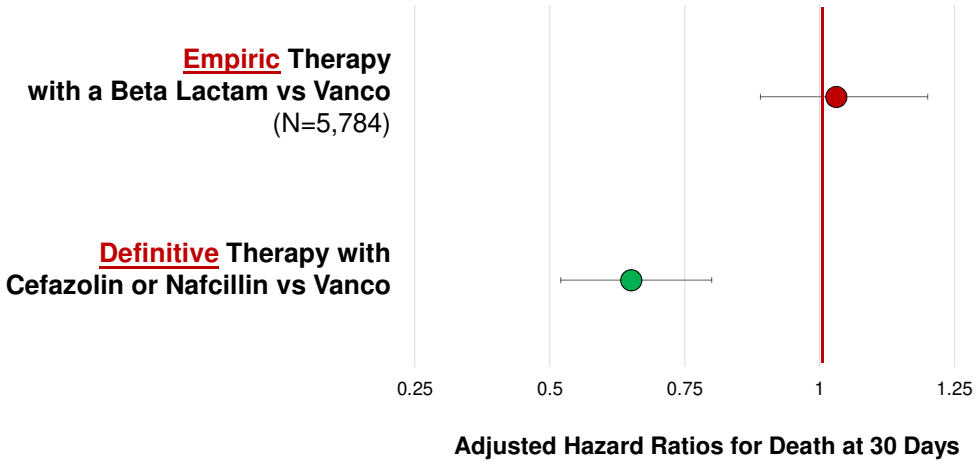
Escrihuela-Vidal, *Clin Micro Infection* 2023;29:498-505

What's the best drug to treat MSSA?

(methicillin-susceptible *Staph aureus)*

Vanco vs Beta Lactams

*Retrospective analysis of all VA patients with positive blood cultures for **MSSA**, 2003-2010, N=16,973*

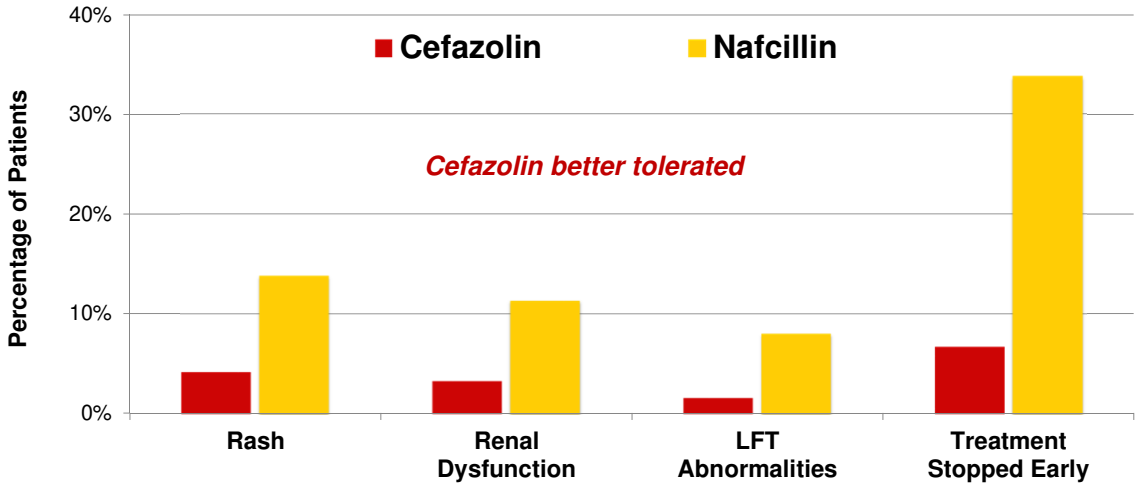


McDanel, Clin Infect Dis 2015;61:361-7

Which beta-lactam should we use? Cefazolin or nafcillin?

Tolerability of Cefazolin vs Nafcillin

Retrospective analysis of 485 patients with MSSA infections

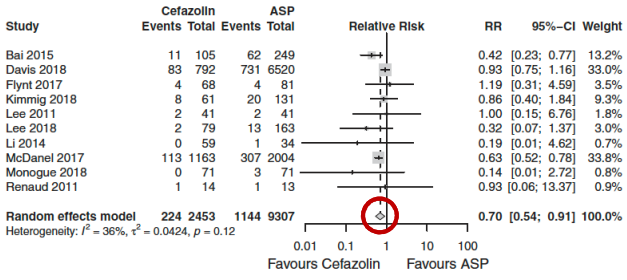


Youngster, *Clin Infect Dis* 2014;59:369-75

Cefazolin vs Nafcillin for MSSA Bacteremia

Meta-analysis of 14 observational studies, 11,760 patients

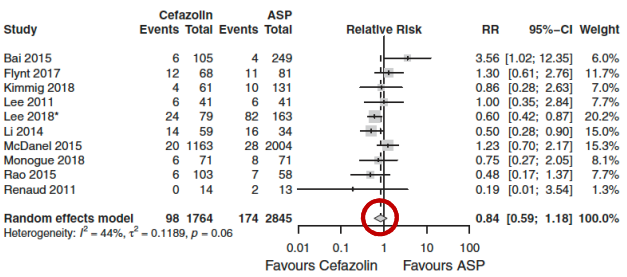
30d all cause mortality



Cefazolin associated with lower all-cause mortality

RR 0.70 (95% CI 0.54-0.91)

Treatment failure or relapse



No difference in treatment failure or relapse

RR 0.84 (95% CI 0.59-1.18)

Weis, *Clin Micro Infection* 2019;25:818-827

What about ceftriaxone for MSSA bacteremia?

Ceftriaxone for MSSA Bacteremia: Mixed Results

Study 1: OPAT for MSSA bacteremia

- Retrospective analysis of 243 patients with MSSA bacteremia referred for OPAT
  - 61% discharged on ceftriaxone
  - 39% discharged on cefazolin or oxacillin
- **No differences** in
  - Antibiotic intolerance (4.2 vs 4.1%)
  - Microbiological failure (6.3 vs 6.1%)
  - Readmissions for MSSA (10.5 vs 8.8%)
  - 90-day mortality (7.4 vs 10.1%)

Hamad, *Open Forum Infect Dis* 2020;7(9):ofaa341

Study 2: OPAT for MSSA bacteremia

- Retrospective analysis of 223 patients with MSSA referred for OPAT
  - 17% treated with ceftriaxone
  - 83% treated with cefazolin, nafcillin, or oxacillin
- Treatment failure in 11.7% overall
- **Ceftriaxone: more treatment failure**
  - Hazard ratio 2.7 (95% CI 1.2-6.1)

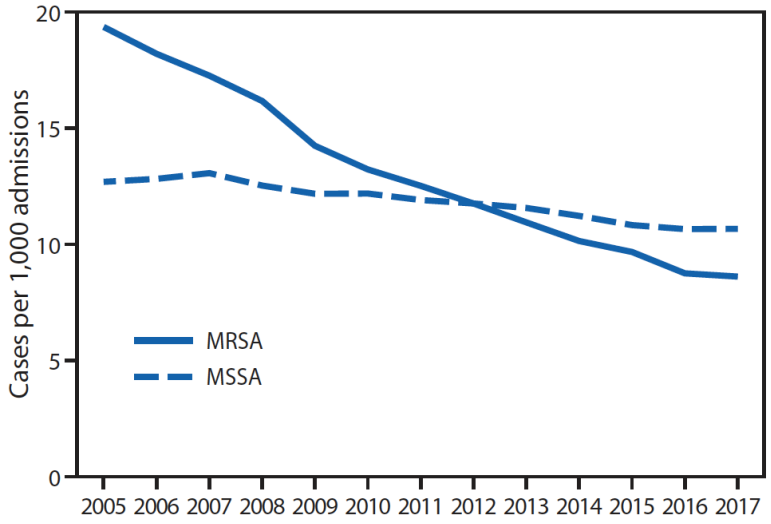
Yetmar, *Eur J Clin Micro Infect Dis* 2023;42:423-430

Case Study Continued

- The following day the patient shows further signs of improvement.
- She is more alert, less confused, and her temperature curve is normalizing.
- You review her blood cultures from admission:
  - 4/4 bottles were positive for MRSA
  - Yesterday's blood cultures are negative thus far.
  - Another set of blood cultures for today is pending.

Incidence of MRSA steadily decreasing

Incidence of Staph aureus infections in hospitalized patients, 130 VA hospitals, 2005-2017



MMWR 2019;68:1-6

What's the best drug for MRSA?

www.hospira.com

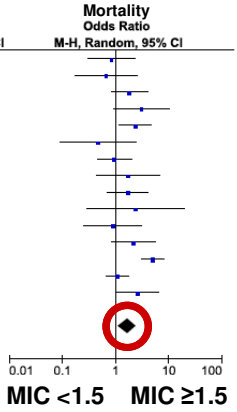
Vanco MIC and Mortality

Meta-analysis #1

Study or Subgroup	MIC ≥1.5 Events	MIC ≥1.5 Total	MIC <1.5 Events	MIC <1.5 Total	Weight	Odds Ratio M-H, Random, 95% CI
Bae et al (12)	13	37	11	28	6.5%	0.84 [0.30, 2.31]
Choi et al (15)	4	34	6	36	4.6%	0.67 [0.17, 2.60]
Haque et al (19)	41	115	10	43	7.9%	1.83 [0.82, 4.08]
Hidayat et al (21)	12	51	4	44	5.3%	3.08 [0.91, 10.37]
Holmes et al (23)	28	94	16	105	8.8%	2.36 [1.18, 4.71]
Lalueza et al (32)	2	13	14	50	3.6%	0.47 [0.09, 2.38]
Liao et al (34)	13	40	46	137	8.3%	0.95 [0.45, 2.02]
Lodise et al (36)	12	66	3	26	4.7%	1.70 [0.44, 6.61]
Musta et al (43)	60	206	7	36	7.4%	1.70 [0.71, 4.10]
Neuner et al (45)	39	186	1	10	2.5%	2.39 [0.29, 19.42]
Schweizer et al (50)	46	341	3	20	5.1%	0.88 [0.25, 3.13]
Soriano et al (52)	37	130	6	38	6.9%	2.12 [0.82, 5.49]
Takesue et al (53)	33	97	62	662	10.4%	4.99 [3.04, 8.18]
van Hal et al (54)	38	117	73	236	10.6%	1.07 [0.67, 1.73]
Wang et al (55)	13	26	27	97	7.3%	2.59 [1.07, 6.30]
Total (95% CI)		**1553**		**1568**	**100.0%**	**1.64 [1.14, 2.37]**
Total events	391		289			

Heterogeneity: Tau² = 0.27; Chi² = 34.07, df = 14 (P = .002); I² = 59%

Test for overall effect: Z = 2.65 (P = .008)



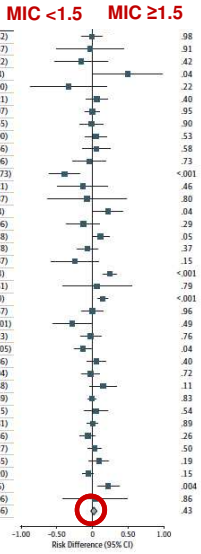
OR for Death: 1.64
(95% CI 1.14-2.37)

***Clin Infect Dis* 2012**;54:755-71

Vanco MIC and Mortality

Meta-analysis #2

Source	High MIC, No. Deaths	High MIC, No. Total	Low MIC, No. Deaths	Low MIC, No. Total	Risk Difference (95% CI)
Schwaber et al,[18] 2003	16	61	23	87	-0.002 (-0.146 to 0.142)
Howden et al,[20] 2004	4	7	6	10	-0.029 (-0.505 to 0.447)
Charles et al,[13] 2004	1	5	17	48	-0.154 (-0.530 to 0.222)
Neoh et al,[22] 2007	2	2	8	16	0.500 (0.016 to 0.984)
Maor et al,[21] 2007	2	4	10	12	-0.333 (-0.867 to 0.200)
Lodise et al,[24] 2008	12	66	3	26	0.066 (-0.088 to 0.221)
Soriano et al,[23] 2008	26	92	90	322	0.003 (-0.101 to 0.107)
Liao et al,[31] 2008	13	40	46	137	-0.011 (-0.176 to 0.155)
Musta et al,[30] 2009	14	43	67	242	0.049 (-0.102 to 0.200)
Maor et al,[29] 2009	14	27	103	223	0.057 (-0.143 to 0.256)
Bae et al,[26] 2009	13	37	11	28	-0.042 (-0.279 to 0.196)
Price et al,[11] 2009	1	20	11	25	-0.390 (-0.607 to -0.173)
Fong et al,[27] 2009	5	10	19	30	-0.133 (-0.488 to 0.221)
Jang et al,[28] 2009	1	3	13	32	-0.073 (-0.633 to 0.487)
Wang et al,[38] 2010	13	26	27	97	0.222 (0.010 to 0.434)
Lalueza et al,[32] 2010	2	13	14	50	-0.126 (-0.358 to 0.106)
Neuner et al,[36] 2010	21	76	19	120	0.118 (-0.002 to 0.238)
Lin et al,[34] 2010	24	60	78	167	-0.067 (-0.212 to 0.078)
Lewis et al,[33] 2010	0	3	34	139	-0.245 (-0.576 to 0.087)
Takesue et al,[37] 2010	33	97	62	662	0.247 (0.150 to 0.343)
Moore et al,[35] 2010	4	6	6	10	0.067 (-0.418 to 0.551)
Holmes et al,[42] 2011	48	179	42	344	0.146 (0.073 to 0.220)
Walraven et al,[47] 2011	21	69	21	70	0.004 (-0.148 to 0.157)
deSanctis et al,[41] 2011	0	4	26	93	-0.280 (-0.558 to -0.001)
Khatib et al,[44] 2011	8	36	60	245	-0.023 (-0.169 to 0.123)
van Hal et al,[46] 2011	8	47	66	221	-0.128 (-0.252 to -0.005)
Honda et al,[43] 2011	26	112	9	51	0.056 (-0.075 to 0.186)
Clemens et al,[40] 2011	2	24	10	94	-0.023 (-0.150 to 0.104)
Aguado et al,[39] 2011	6	23	8	76	0.156 (-0.037 to 0.348)
Schweizer et al,[45] 2011	82	619	27	195	-0.006 (-0.061 to 0.049)
Yeh et al,[52] 2012	27	62	30	78	0.051 (-0.113 to 0.215)
Han et al,[48] 2012	21	134	39	258	0.006 (-0.070 to 0.081)
Rojas et al,[51] 2012	102	240	59	121	-0.063 (-0.171 to 0.046)
Miller et al,[50] 2012	36	111	170	583	0.033 (-0.062 to 0.127)
Chen et al,[48] 2012	19	53	63	238	0.094 (-0.047 to 0.235)
Gasch et al,[53] 2013	69	237	110	315	-0.058 (-0.136 to 0.020)
Yoon et al,[55] 2014	36	87	9	47	0.222 (0.069 to 0.375)
Kan et al,[54] 2014	2	5	14	39	0.041 (-0.414 to 0.496)
Overall (z score = 0.797; P = .43; T² = 0.007)	734	2740	1430	5551	0.016 (-0.023 to 0.056)



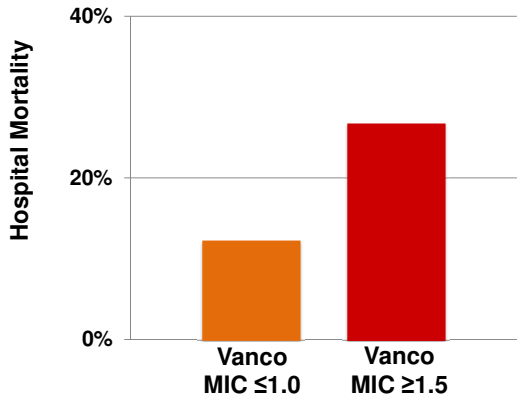
No difference!

JAMA 2014;312:1552-1564

Vanco MIC and Outcomes for MSSA

266 patients with MSSA bacteremia (8 hospitals), all treated with flucloxacillin

Higher mortality if vanco MIC ≥1.5 even though patients treated with B-lactam!

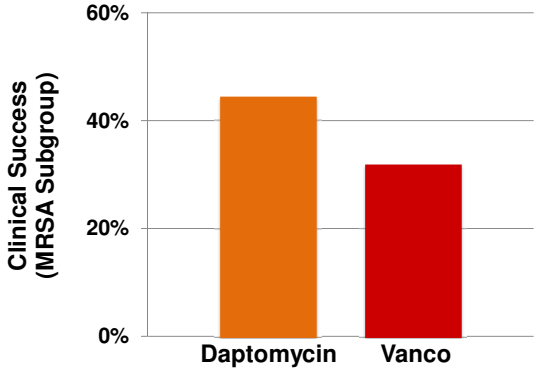


Holmes, *J Infect Dis* 2011;204:340-7

Vancomycin vs Daptomycin

Randomized trial of daptomycin vs standard therapy for Staph aureus bacteremia & endocarditis, N=124

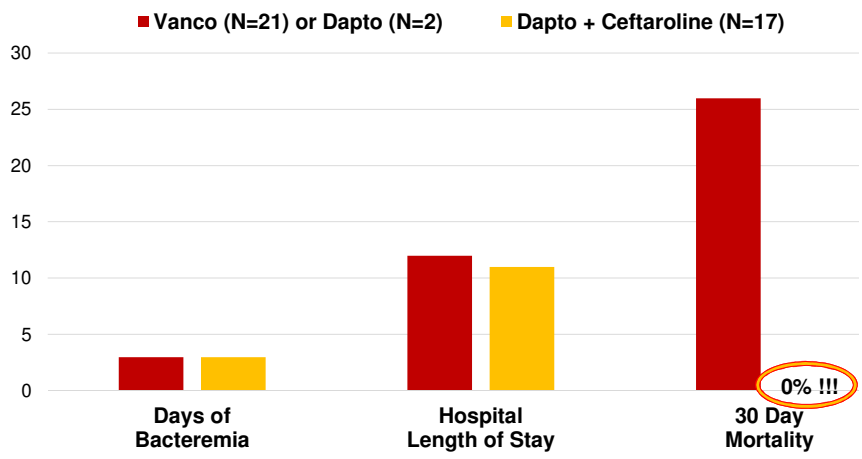
No difference!



Fowler, *N Engl J Med* 2006:355:653-665

What about Ceftaroline?

40 patients with MRSA bacteremia randomized to vancomycin or daptomycin versus daptomycin + ceftaroline; trial stopped early due to unexpected high mortality rate in vanco/dapto arm



Important Caveats

Tiny sample size

Important imbalance between groups:

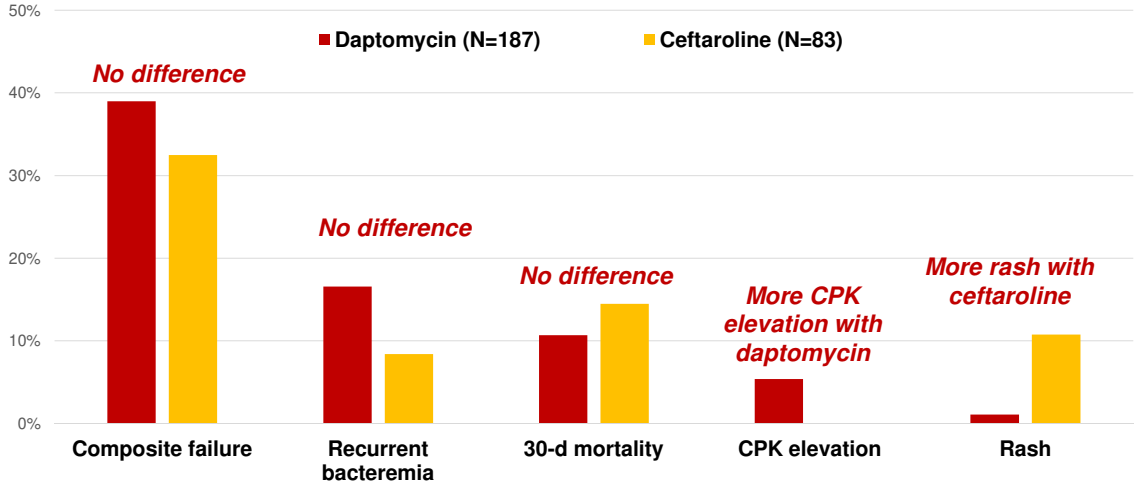
vanco/dapto group with more diabetes, ESRD, and cancer

Is the benefit (if real) due to dapto, ceftaroline, or both?

Geriak, *Antimicrobial Agents & Chemotherapy* 2019;63(5):e02483-18

Ceftaroline vs Daptomycin: Observational Data

Retrospective analysis of 270 patients with MRSA bacteremia, 83 treated with ceftaroline, 187 with daptomycin, outcomes compared using inverse probability of treatment weighting, 10 hospitals, 2010-2017



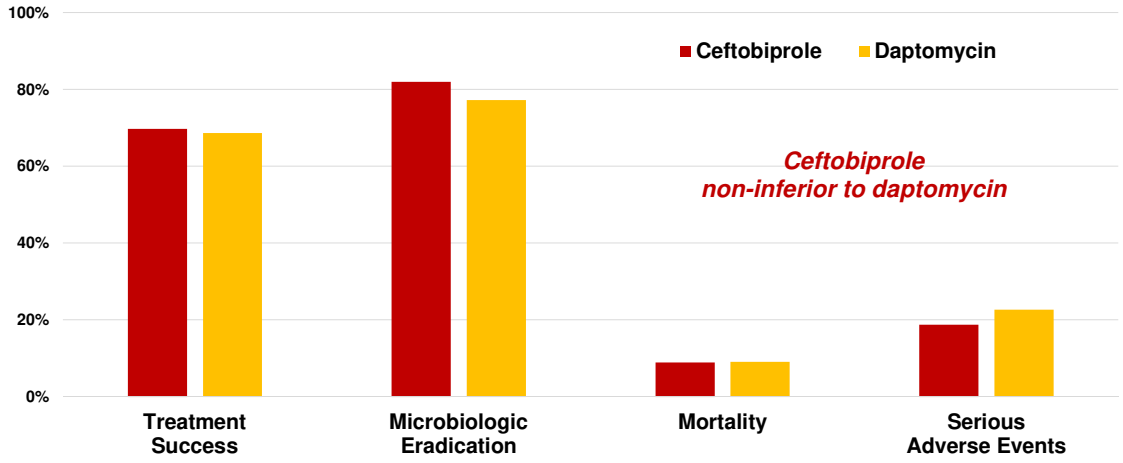
Zasowski, *Open Forum Infect Dis* 2022; doi.org/10.1093/ofid/ofab606

What about Ceftobiprole?*

*not yet FDA approved

390 patients with complicated Staph aureus bacteremia randomized to ceftobiprole vs daptomycin.

Complicated = bacteremia for ≥3d, hemodialysis, bacteremia secondary to soft-tissue infection, abdominal abscess, osteoarticular infection, septic thrombophlebitis, septic pulmonary embolus, epidural or cerebral abscess, or right-sided endocarditis

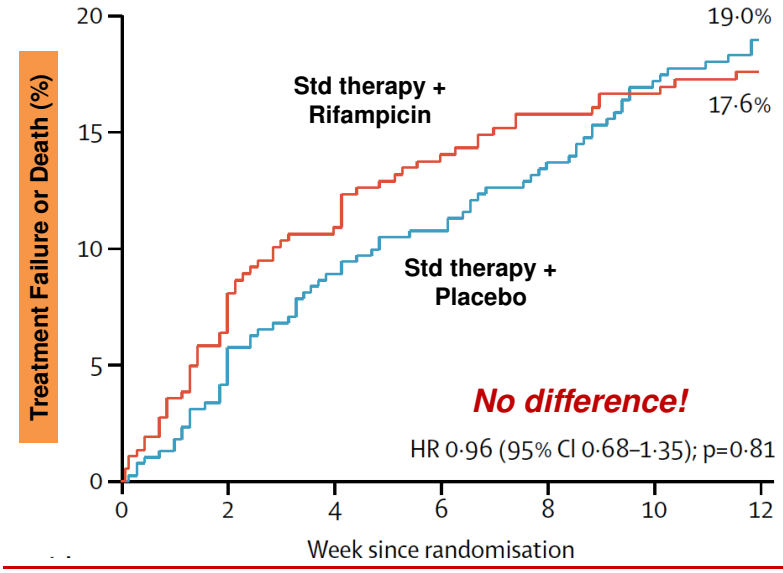


Holland, *NEJM* 2023;389:1390-1401

Would it help if we added rifampin?

Adjunctive Rifampicin for Staph aureus Bacteremia

758 patients with Staph aureus bacteremia randomized to standard therapy + rifampicin or placebo



Notes

- 94% had MSSA infections
- Standard therapy was flucloxacillin for 82% of patients
- Adverse events leading to changes in antibiotics more common in the rifampicin group
  (GI intolerance and AKI)

Thwaites, *Lancet* 2018;391:668-678

Do we need to get a transesophageal echocardiogram?

Endocarditis Prediction Rules

POSITIVE Cutoff: >4	PREDICT Cutoff: ≥2	VIRSTA Cutoff: ≥3
Time-to-positivity <9h (5) Time-to-positivity 9-11h (3) Time-to-positivity 11-13h (2) IV drug use (3) Emboli (6) Predisposing ht dz (5)	ICD (2) Pacer (3) Community-acquired (2) Healthcare-acquired (1) >72h bacteremia (2)	Emboli (5) Meningitis (5) ICD or hx endocarditis (4) Native valve disease (3) IV drug use (4) >48h bacteremia (3) Community or healthcare-acq (2) Sepsis or septic shock (1) CRP >190 (1)
Sensitivity: 78% NPV: 93%	Sensitivity: 85% NPV: 95%	Sensitivity: 99% NPV: 99%

van der Vaart, *Clin Infect Dis* 2022;74:1442-9

Nosocomial *Staph aureus* Bacteremia

- **Does the patient have any of the following?**
  - Bacteremia persisting for >4 days
  - Permanent intracardiac device
  - Hemodialysis dependence
  - Spinal infection
  - Osteomyelitis
- If no, then TEE unnecessary

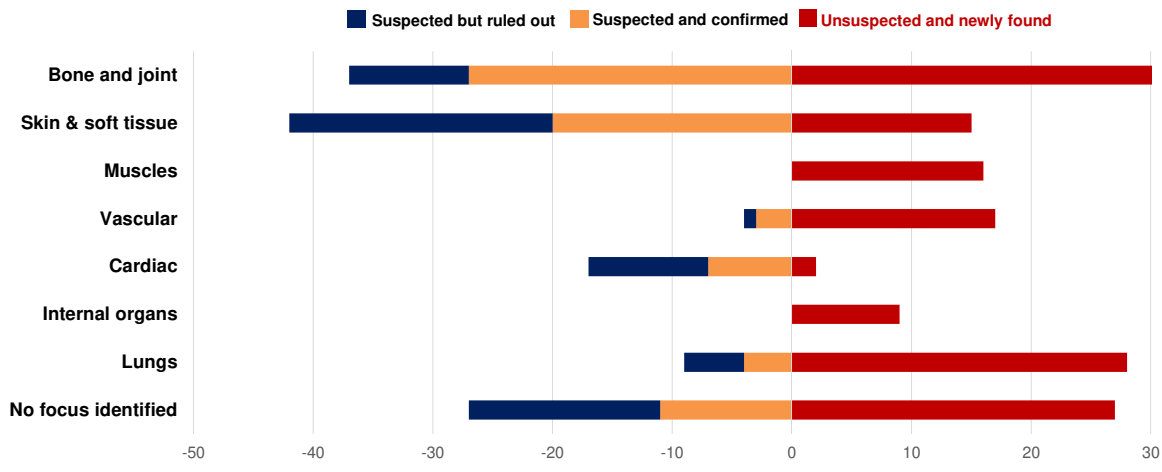
(Derived from retrospective analysis of 2 multicenter cohorts of patients with nosocomial *Staph aureus* bacteremia, N=706)

Clin Infect Dis 2011;53:1-9

Should we get a FDG-PET/CT scan?

FDG-PET/CT for *Staph aureus* bacteremia

149 patients with 151 episodes of Staph aureus bacteremia referred for FDG-PET and compared to 151 matched controls with Staph aureus bacteremia who did not go for PET

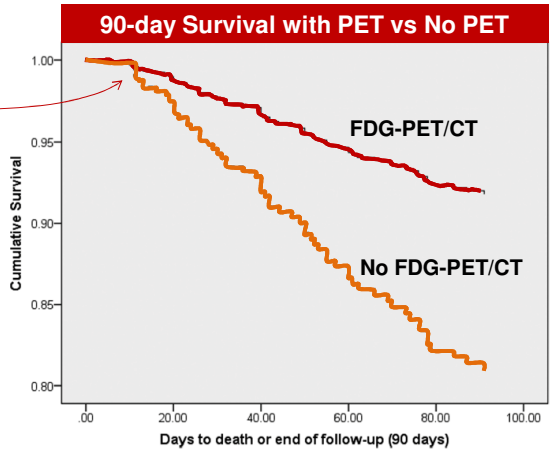


Ghanem-Zoubi, *Clin Infect Dis* 2021;73:e3859-66

FDG-PET/CT for *Staph aureus* bacteremia

149 patients with 151 episodes of Staph aureus bacteremia referred for FDG-PET and compared to 151 matched controls with Staph aureus bacteremia who did not go for PET

Median 11 days until FDG-PET obtained



Ghanem-Zoubi, *Clin Infect Dis* 2021;73:e3859-66

Case Study Continued

- A transthoracic echocardiogram shows decreased ejection fraction, moderate mitral regurgitation, but no vegetations on either the AICD leads or valves.
- A transesophageal echocardiogram, however, does confirm a 1.2cm vegetation on the mitral valve. No vegetations are seen on the AICD leads.
- The AICD generator and leads are removed.

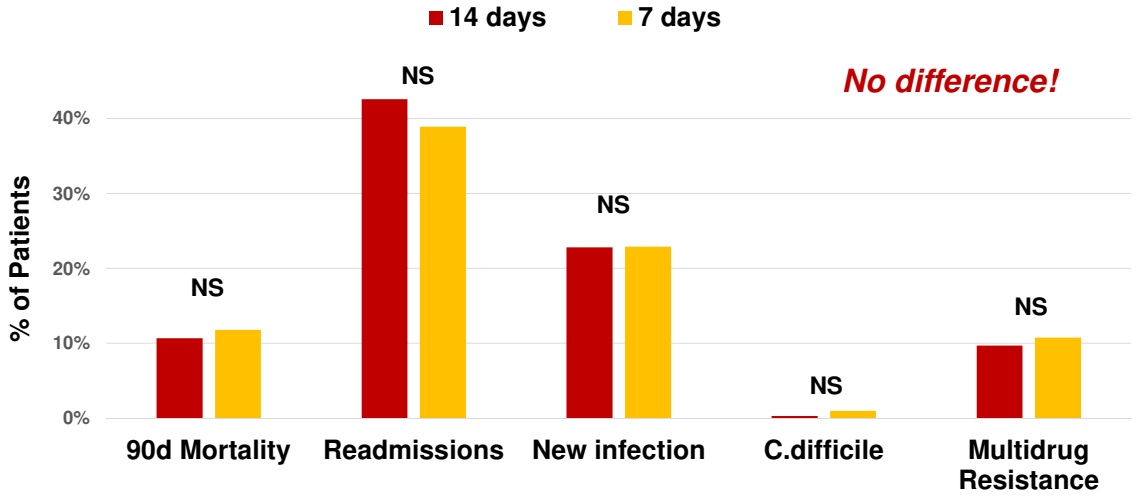
How long should we treat for?

Depends on the Syndrome & Pathogen

- Some syndromes require longer courses:
  - Endocarditis
  - Osteomyelitis
  - Septic arthritis
  - Undrainable abscess
  - Unremovable prosthetic device infection
  - Severe immunosuppression (e.g. ANC <500 cells/mm^3)
- Some pathogens often require longer courses:
  - *Staphylococcus aureus*
    - *4 weeks default, 2 weeks if uncomplicated, 6 weeks if endovascular infection*

Duration of Abx for Gram Negative Bacteremia: RCT 1

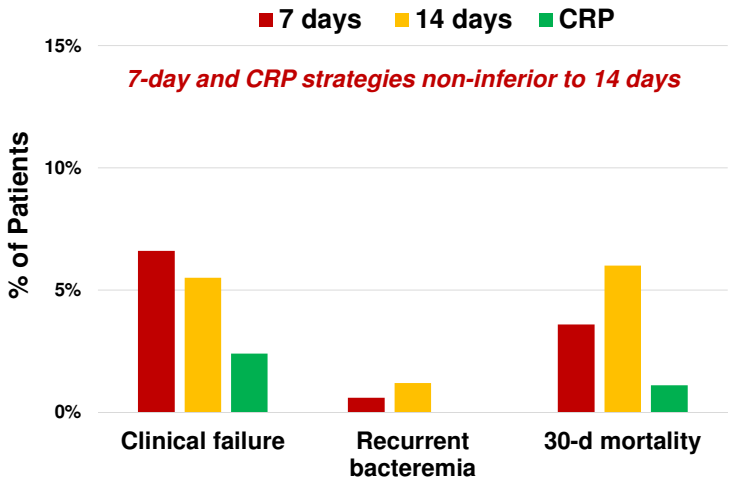
604 patients randomized to 7 vs 14 days of antibiotics for Gram negative bacteremia

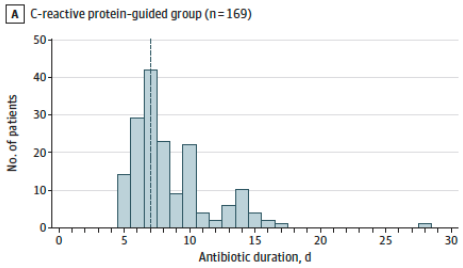


Yahav, *Clin Infect Dis* 2019;69:1091-1098

Duration of Abx for Gram Negative Bacteremia: RCT 2

504 patients randomized to 7 days vs 14 days vs CRP-guided antibiotics for Gram negative bacteremia
CRP group: abx stopped when CRP dropped 75% from peak and patient afebrile ≥48h

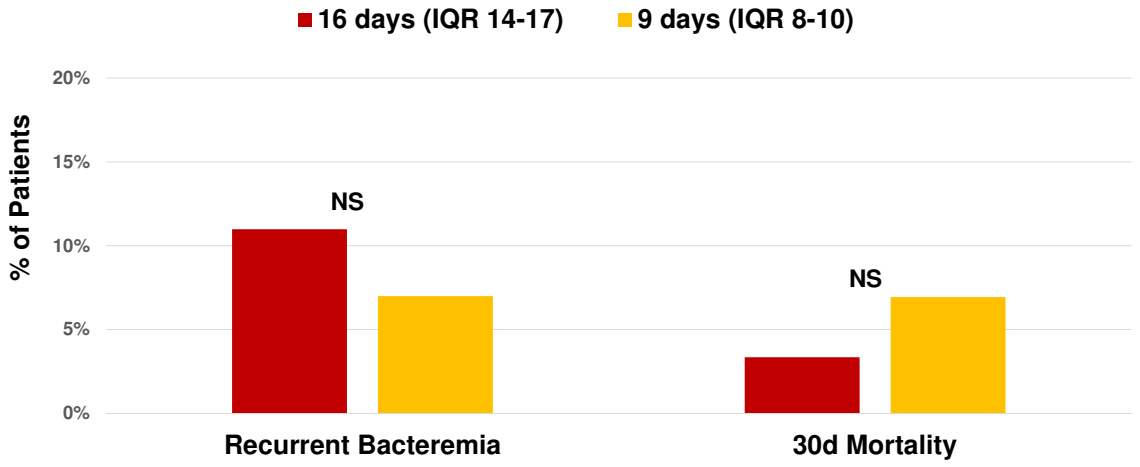




von Dach, *JAMA* 2020;323:2160-2169

Duration of Abx for *Pseudomonas* bacteremia: Propensity Analysis

Propensity-matched analysis of 249 patients from 5 hospitals with Pseudomonas bacteremia



Fabre, *Clin Infectious Dis* 2019;69:2011-2014

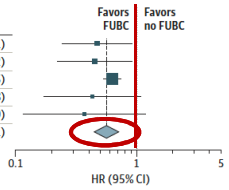
Should we get follow-up blood cultures?

Follow-up Blood Cultures for Gram-Negative Bacteremia

Meta-analysis of 15 observational studies assessing association between follow-up blood cultures and mortality in patients with gram-negative bloodstream infections, N=3495 patients

Association between OBTAINING follow-up blood cultures and mortality

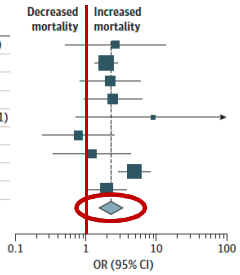
Source	HR (95% CI)
Amipara et al,[9] 2021	0.47 (0.24-0.91)
Giannella et al,[7] 2020	0.45 (0.22-0.92)
Maskarinec et al,[5] 2020	0.63 (0.53-0.75)
Green et al,[21] 2021	0.43 (0.17-1.08)
Mitaka et al,[22] 2021	0.37 (0.12-1.19)
Total	0.56 (0.45-0.71)
Heterogeneity: $\chi^2_4 = 2.57$ ($P = .63$); $I^2 = 0\%$	



***Obtaining* follow-up cultures associated with 44% lower hazard ratio for death (95% CI 0.45-0.71)**

Association between POSITIVE follow-up blood cultures and mortality

Source	OR (95% CI)
Amipara et al,[9] 2021	2.64 (0.51-13.55)
Maskarinec et al,[5] 2020	1.93 (1.33-2.80)
Chan et al,[11] 2021	2.22 (0.83-5.93)
Wiggers et al,[8] 2016	2.40 (0.93-6.19)
Groft et al,[32] 2021	9.00 (0.71-113.81)
Spaziante et al,[28] 2020	0.78 (0.24-2.53)
Mitaka et al,[29] 2020	1.21 (0.34-4.31)
Kim et al,[30] 2022	4.87 (2.90-8.17)
Kang et al,[31] 2013	1.98 (1.03-3.81)
Total	2.27 (1.54-3.34)
Heterogeneity: $\chi^2_8 = 14.48$ ($P = .07$); $I^2 = 45\%$	



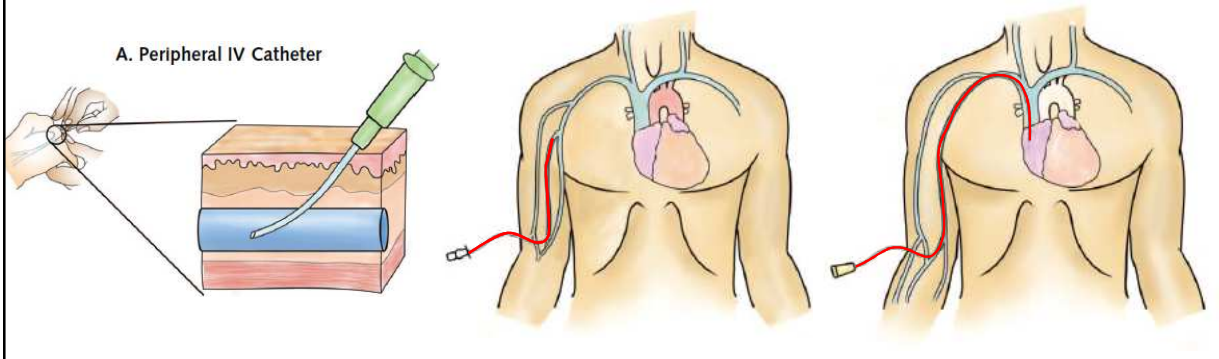
***Positive* follow-up cultures associated with a 2.3-fold higher odds of death (95% CI 1.54-3.34)**

Thaden, *JAMA Network Open* 2022;5(9):e2232576

Should we place a PICC line?

MAGIC Guidelines

<5 days	6 to 14 days	>14 days

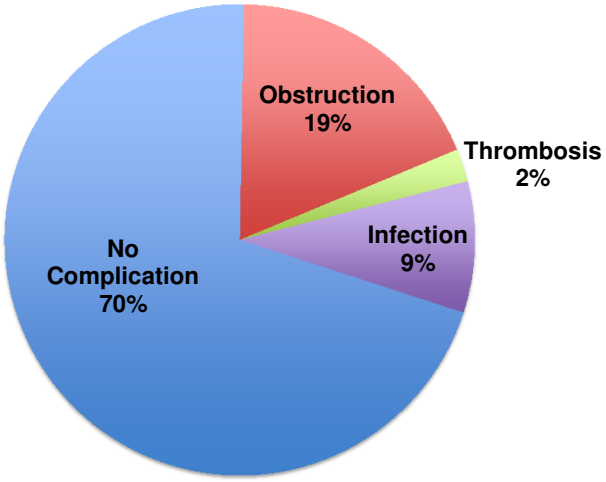


Peripheral IV **Midline** **PICC Line**

Annals Intern Med 2015;163:S1-S39

PICC Line Complications

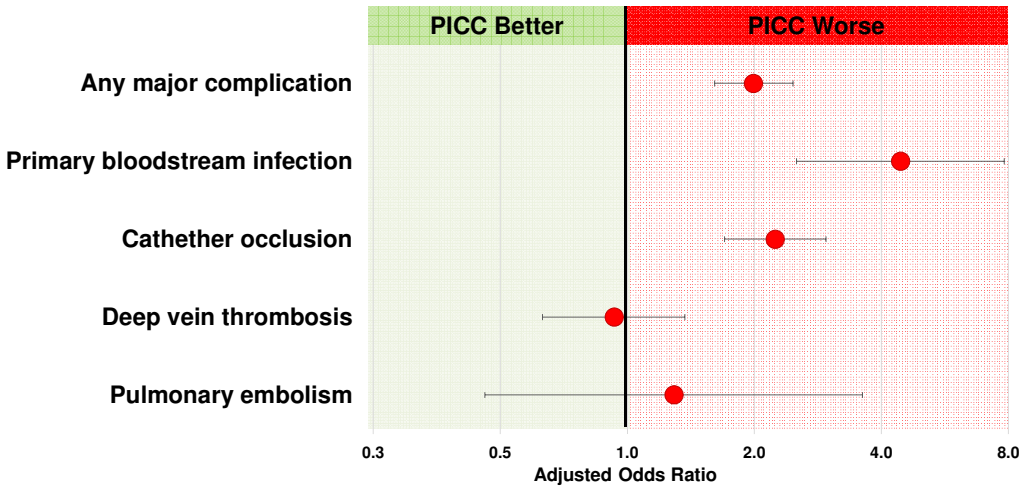
Prospective Surveillance of 222 PICC Lines Placed by IR in a French Hospital. Median Duration 17 days.



Medecine et Maladies Infectieuses 2013;43:350

PICC lines vs Midlines

Complication rates in 5758 patients with PICCs vs 5105 with midlines, all placed for difficult venous access or short-term intravenous antibiotics, 48 Michigan hospitals, Dec 2017-Jan 2020



Swaminathan, *JAMA IM* 2022;182:50-58

Can we treat with orals?

TREATMENT OF RIGHT-SIDED STAPHYLOCOCCUS AUREUS ENDOCARDITIS IN INTRAVENOUS DRUG USERS WITH CIPROFLOXACIN AND RIFAMPICIN

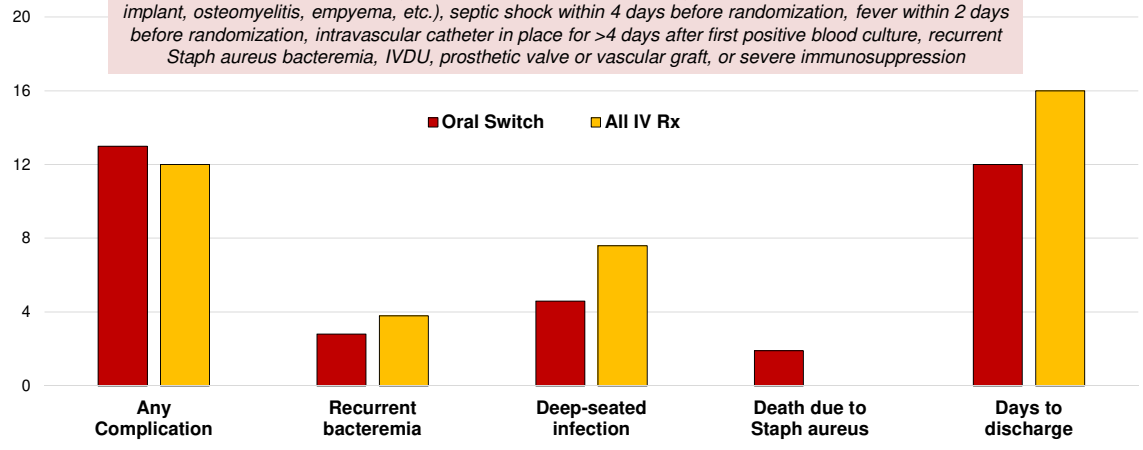
- 14 IV drug users with right-sided *Staph aureus* endocarditis treated with ciprofloxacin + rifampin
  - Cipro given IV x 1 week then 750mg PO x 3 weeks
  - Rifampin 300mg PO bid x 4 weeks
- 10 completed therapy – all were cured

The Lancet 1989;8671:1071

Early switch to orals for *Staph aureus bacteremia*

213 patients with uncomplicated Staph aureus bacteremia randomized to orals vs IV abx after 5-7 days of IV abx. All patients treated for a total of 14 days. Most common orals were TMP-SMX (58%) and clindamycin (32%).

Uncomplicated = no signs or symptoms of deep-seated focus (e.g. endocarditis, pneumonia, infected implant, osteomyelitis, empyema, etc.), septic shock within 4 days before randomization, fever within 2 days before randomization, intravascular catheter in place for >4 days after first positive blood culture, recurrent Staph aureus bacteremia, IVDU, prosthetic valve or vascular graft, or severe immunosuppression



Kaasch, SABATO Trial, *medRxiv* 2023; doi.org/10.1101/2023.07.03.23291932

Partial Oral vs IV Antibiotics for Endocarditis

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D., Sabine U. Gill, M.D., Ph.D., Trine Madsen, M.D., Ph.D., Hanne Elming, M.D., Ph.D., Kaare T. Jensen, M.D., Ph.D., Niels E. Bruun, M.D., D.M.Sc., Dan E. Hofsten, M.D., Ph.D., Kurt Fursted, M.D., D.M.Sc., Jens J. Christensen, M.D., D.M.Sc., Martin Schultz, M.D., Christine F. Klein, M.D., Emil L. Fosbøl, M.D., Ph.D., Flemming Rosenvinge, M.D., Henrik C. Schønheyder, M.D., D.M.Sc., Lars Køber, M.D., D.M.Sc., Christian Torp-Pedersen, M.D., D.M.Sc., Jannik Helweg-Larsen, M.D., D.M.Sc., Niels Tønder, M.D., D.M.Sc., Claus Moser, M.D., Ph.D., and Henning Bundgaard, M.D., D.M.Sc.

ABSTRACT

BACKGROUND
Patients with infective endocarditis on the left side of the heart are typically treated with intravenous antibiotic agents for up to 6 weeks. Whether a shift from intravenous to oral antibiotics once the patient is in stable condition would result in efficacy and safety similar to those with continued intravenous treatment is unknown.

METHODS
In a randomized, noninferiority, multicenter trial, we assigned 400 adults in stable condition who had endocarditis on the left side of the heart caused by streptococcus, *Enterococcus faecalis*, *Staphylococcus aureus*, or coagulase-negative staphylococci and who were being treated with intravenous antibiotics to continue intravenous treatment (199 patients) or to switch to oral antibiotic treatment (201 patients). In all patients, antibiotic treatment was administered intravenously for at least 10 days. If feasible, patients in the orally treated group were discharged to outpatient treatment. The primary outcome was a composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with the primary pathogen, from the time of randomization until 6 months after antibiotic treatment was completed.

RESULTS
After randomization, antibiotic treatment was completed after a median of 19 days (interquartile range, 14 to 25) in the intravenously treated group and 17 days (interquartile range, 14 to 25) in the orally treated group (P=0.48). The primary composite outcome occurred in 24 patients (12.1%) in the intravenously treated group and in 18 (9.0%) in the orally treated group (between-group difference, 3.1 percentage points; 95% confidence interval, −3.4 to 9.6; P=0.40), which met noninferiority criteria.

CONCLUSIONS
In patients with endocarditis on the left side of the heart who were in stable condition, changing to oral antibiotic treatment was noninferior to continued intravenous antibiotic treatment. (Funded by the Danish Heart Foundation and others; POET ClinicalTrials.gov number, NCT01375257.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. Bundgaard at the Department of Cardiology B 2141, the Heart Center, Rigshospitalet, Copenhagen University Hospital, Blegdamsvej 9, 2100 Copenhagen, Denmark, or at henning.bundgaard@regionh.dk.

Drs. Iversen, Ihlemann, Hofsten, Fosbøl, Køber, and Bundgaard are members of Copenhagen Health Science Partners.

This article was published on August 28, 2018, at NEJM.org.

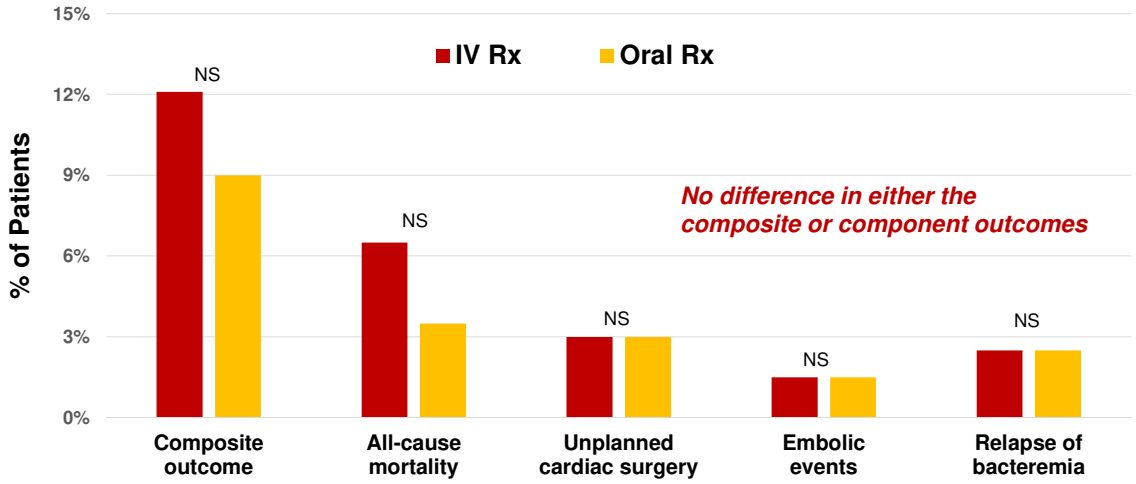
DOI: 10.1056/NEJMoa1808312

- Multicenter, randomized trial from Denmark
- 600 patients with left-sided endocarditis
  - Streptococcus 48%, Rx amox + rifampin, amp + moxifloxacin
  - *Enterococcus faecalis* 24%, Rx amox + moxifloxacin
  - *Staph aureus* 22%, Rx diclox-rif or amox-rif
  - Coag-negative Staph 6%, Rx linezolid + fusidic acid or rifampin
  - 27% with prosthetic valves, 9% with pacemakers
- All patients received at least 10d IV antibiotics then randomized to continue IV antibiotics vs switch to oral antibiotics
- Primary outcome: composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia
- Doses high: amox 1g PO qid, diclox 1g PO qid

Iversen, *N Engl J Med* 2019;380:415-424

Partial Oral vs IV Antibiotics for Endocarditis

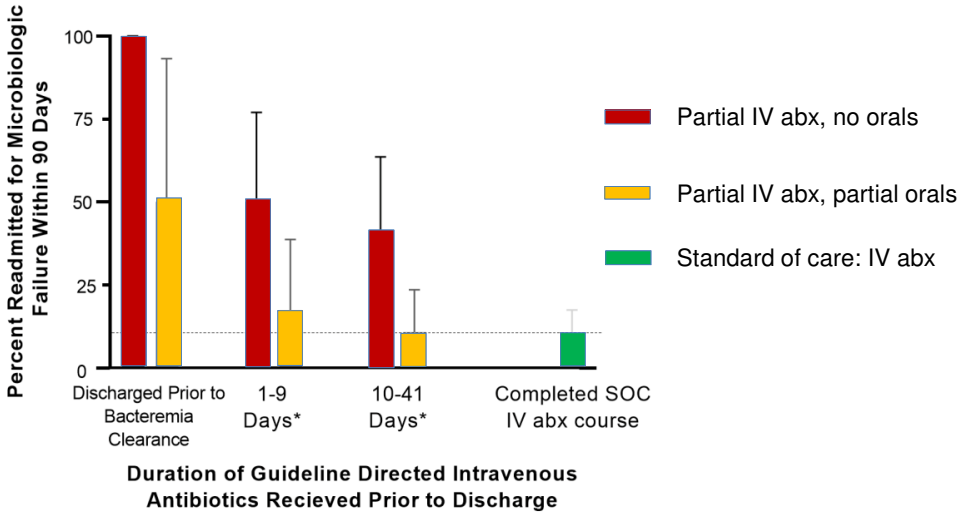
400 patients randomized to IV vs oral antibiotics for left-sided endocarditis following 10d IV Rx



Iversen, *N Engl J Med* 2019;380:415-424

Orals for complicated *Staph aureus* bacteremia: real world

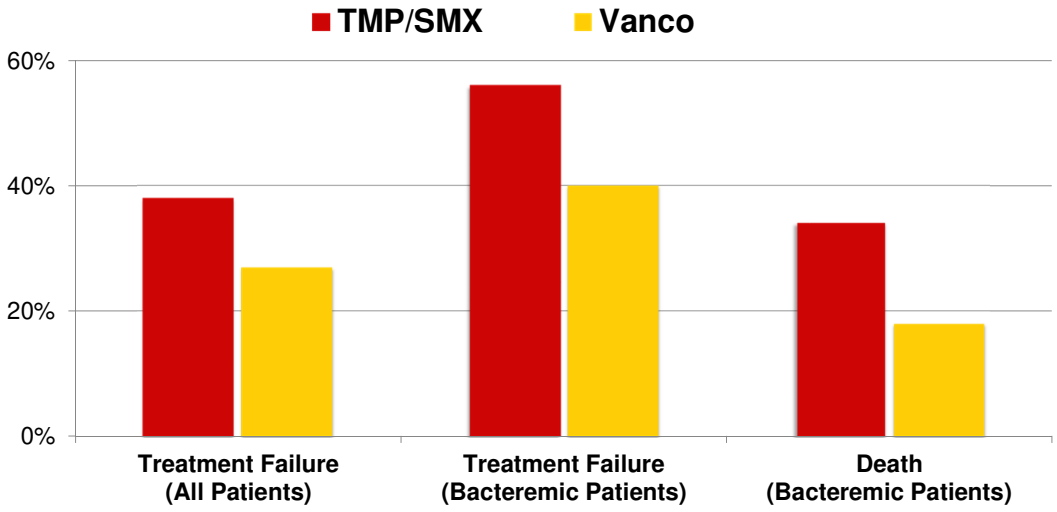
238 patients who inject drugs hospitalized with complicated Staph aureus bacteremia (endocarditis, vertebral osteomyelitis, septic arthritis, epidural abscess), Barnes Jewish Hospital, 2016-2021



Wildenthal, *Clin Infect Dis* 2023;76:487-496

TMP/SMX vs Vanco for Serious MRSA Infections

252 patients with MRSA infections randomized to TMP/SMX 320/1600mg q12h (PO or IV) vs vanco 1g IV q12h



Paul, *BMJ* 2015;350:h2219

Summary

- One drug sufficient for Pseudomonas bacteremia once susceptibilities known
- Carbapenems preferred for ESBL bacteremia
- Cefazolin is the drug of choice for MSSA bacteremia
- Vancomycin & daptomycin are the drugs of choice for MRSA bacteremia
- High vanco MIC variably associated with worse outcomes;
  not clear if switching to another drug will make a difference
- TEE if community onset *Staph aureus* bacteremia, ≥2-3 days of positive blood cultures, pacer/ICD, structural heart disease, IVDU, hemodialysis, or embolic phenomena
- Treat uncomplicated gram-negative bacteremia for 7 days, *Staph aureus* for 2-6 weeks
- Oral agents for endocarditis seem to be okay after 1-2 weeks IV Rx
- 20-30% complication rate for PICCs; avoid if possible.

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