Oral Antibiotics for Bloodstream Infections

Not All Orals Are Created Equal

Jim Lewis, PharmD, FIDSA

Conflicts of Interest

- JSL: Consultant for Merck, Selux Diagnostics, Innoviva Therapeutics

Special thanks to:

- Ellie Sukerman, MD
- Kristina Bajema, MD, MSc

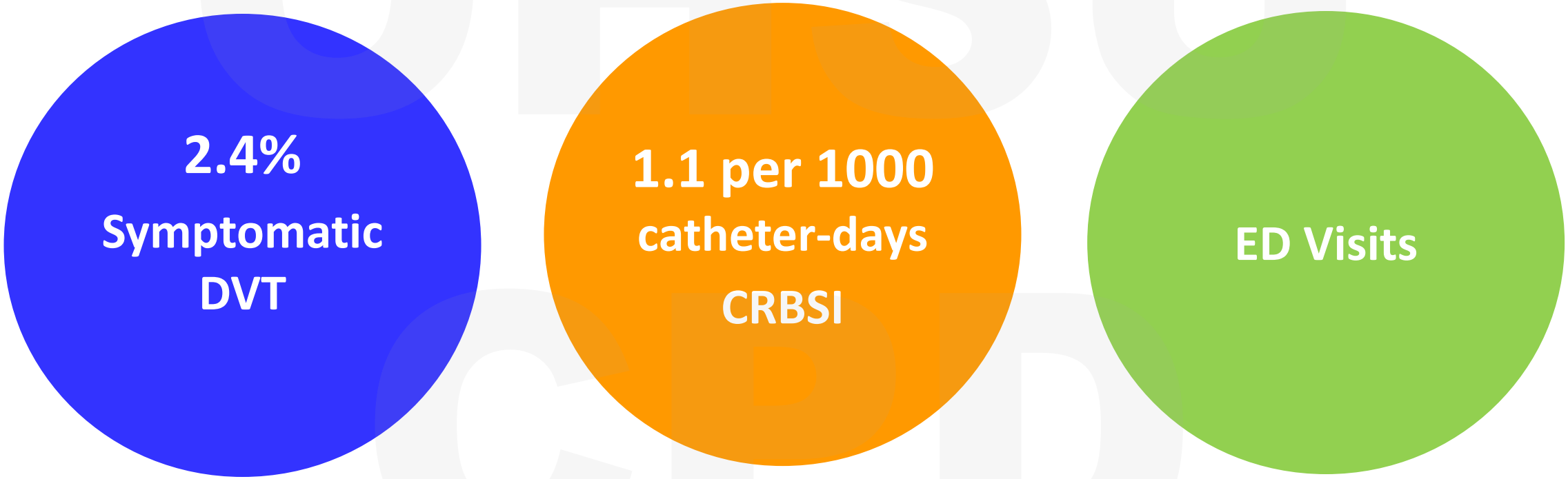
Objectives

1. Understand the general advantages of oral over intravenous antibiotic therapy for bloodstream infections.

2. Understand the appropriate selection and dosing of oral antibiotics for common gram-negative bloodstream infections.

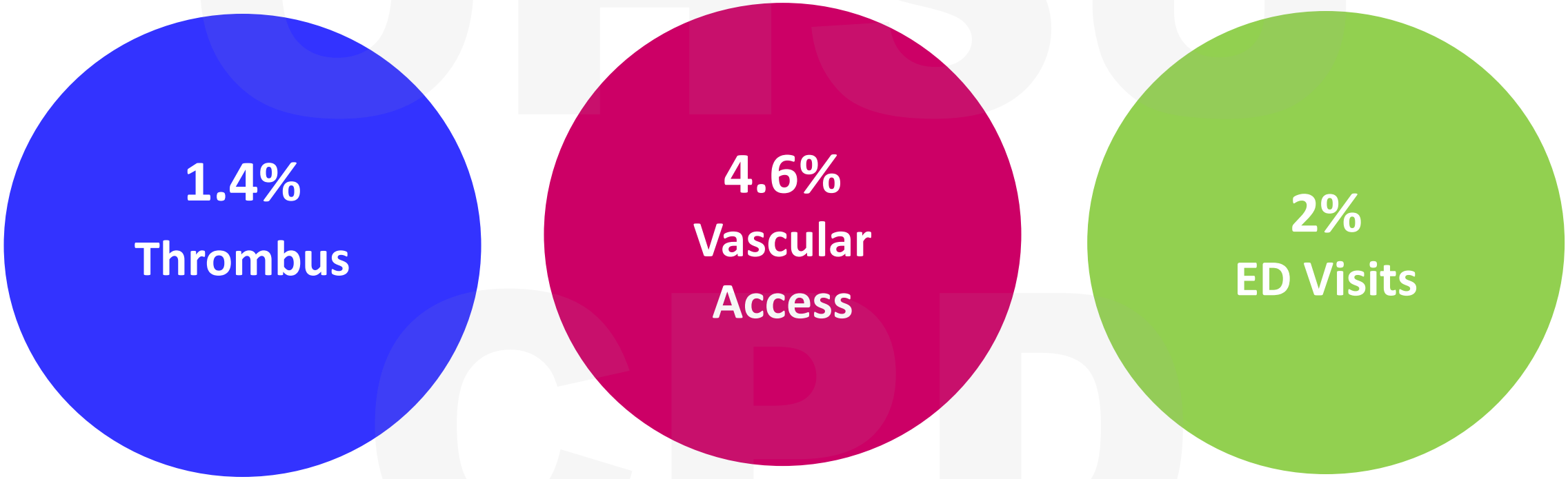
3. Understand the appropriate selection and dosing of oral antibiotics for common gram-positive bloodstream infections.

PICC-associated risks



Balsorano, et al. *J Vasc Access* 2020.
Bhagat H, et al. *Ann Pharmacother* 2023.

OHSU PICC-associated risks



Bhagat H, et al. *Ann Pharmacother* 2023.

Oral versus IV: mean cost-savings $3271 per patient

Bhagat, H et al. *Ann Pharmacother* 2023.

IV antibiotics require more nursing input

22 minutes 5 seconds

80 seconds

Jenkins A. *J Antimicrob Chemother* 2023.

Oral antibiotics are associated with shorter hospital length of stay

Deshpande A et al. *Clin Infect Dis* 2023.
van den Bosch et al. *J Antimicrob Chemother* 2017.

https://www.medplushealth.ca/

The magic isn’t in the IV, the magic is in the PK-PD

Not all orals are created equal...

Oral beta-lactams: Where things get tricky

- Cefazolin 2 g q8h vs cephalexin 500 mg q6h
- Ceftriaxone 2 g daily vs cefpodoxime 200 mg bid
- Cefepime or ceftazidime vs … well…
- Penicillin G 20 MU continuous vs Pen VK 500 mg q6h
- Ampicillin 2 g q4h vs amoxicillin 500 mg q8h
- Oxacillin/Nafcillin 2 g q4h vs dicloxacillin 500 mg q6h
- Pip-tazo vs… well…

IV to PO conversion

- **1:1** - Fluoroquinolones, linezolid, trimethoprim-sulfamethoxazole, clindamycin, tetracyclines
- Amoxicillin, amoxicillin/clavulanic acid, cephalexin, cefadroxil **at high doses**
- Cefpodoxime, cefdinir

Gram Negative Bacteremia

Early IV to PO for Gram negative bacteremia

- Adults with uncomplicated gram negative rod (*E.coli*, Klebsiella spp) bacteremia hospitalized Denmark 2018-21 (n=914)
- Switch to PO within 4 days following blood culture vs continuing IV 5+ days
- 90-day all-cause mortality risk comparable

Table 3. Inverse Probability–Weighted 90-Day Risk of All-Cause Mortality Among Individuals With Gram-Negative Bacteremia Continuing IV Antibiotic Therapy vs Early Switch to Oral Antibiotic Therapy

	90-d Risk of all-cause mortality, % (95% CI)			
Analysis	Early oral switch	Continuing IV treatment	90-d Risk difference (95% CI)	90-d Risk ratio (95% CI)
Intention-to-treat	9.1 (6.7-11.6)	11.7 (9.6-13.8)	−2.5 (−5.7 to 0.7)	0.78 (0.60 to 1.10)
Per-protocol	9.6 (6.7-12.4)	9.7 (7.6-11.8)	−0.1 (−3.4 to 3.1)	0.99 (0.70 to 1.40)

Tingsgard S et al. *JAMA Netw Open* 2024.
Lee IR, et al. *Trials* 2022.
Omrani AS, et al. *Clin Microbiol Infect* 2024.

Open Forum Infectious Diseases

MAJOR ARTICLE

Optimizing the Management of Uncomplicated Gram-Negative Bloodstream Infections: Consensus Guidance Using a Modified Delphi Process

Emily L. Heil,[1] Jacqueline T. Bork,[2] Lilian M. Abbo,[3] Tamar F. Barlam,[4] Sara E. Cosgrove,[5] Angelina Davis,[6] David R. Ha,[7] Timothy C. Jenkins,[8] Keith S. Kaye,[9] James S. Lewis II,[10] Jessica K. Ortwine,[11] Jason M. Pogue,[12] Emily S. Spivak,[13] Michael P. Stevens,[14] Liza Vaezi,[15] and Pranita D. Tamma[16]; for the Antibiotic Stewardship Implementation Collaborative

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Heil EL, et al. *Open Forum Infect Dis* 2021.

General recommendations

- Uncomplicated gram negative bacteremia
  - Source: UTI, intra-abdominal/biliary, catheter-related, pneumonia (without structural disease or empyema/abscess), skin and soft tissue
  - Source control
  - Not immunocompromised
  - Clinical improvement within 72 hours of effective antibiotic treatment
- 7 days is appropriate
- Can treat with oral therapy:
  - Clinical improvement on effective IV
  - Confirmed source
  - Susceptibility confirms available PO option
  - Functional GI tract

Oral antibiotics for uncomplicated gram negative bacteremia

- Ciprofloxacin **500 mg q12h**
- Levofloxacin **750 mg q24h**
- Trimethoprim-sulfamethoxazole **up to 5 mg/kg q12h (1-2 DS q12h)**

- Amoxicillin **1000 mg q8h**
- Amoxicillin/clavulanic acid **875-1000 mg q8h**
- Cephalexin **1000 mg q6h**

- Cefadroxil, cefpodoxime, cefdinir

Oral beta lactams are probably reasonable in genitourinary infections

- 4089 Veterans with *E. coli*, *Klebsiella* spp, or *Proteus* spp bacteremia from a suspected urine source
- 1-5 days IV therapy → oral beta lactam, fluoroquinolone, or TMP-SMX
- No significant difference in 30-day mortality and recurrent bacteremia

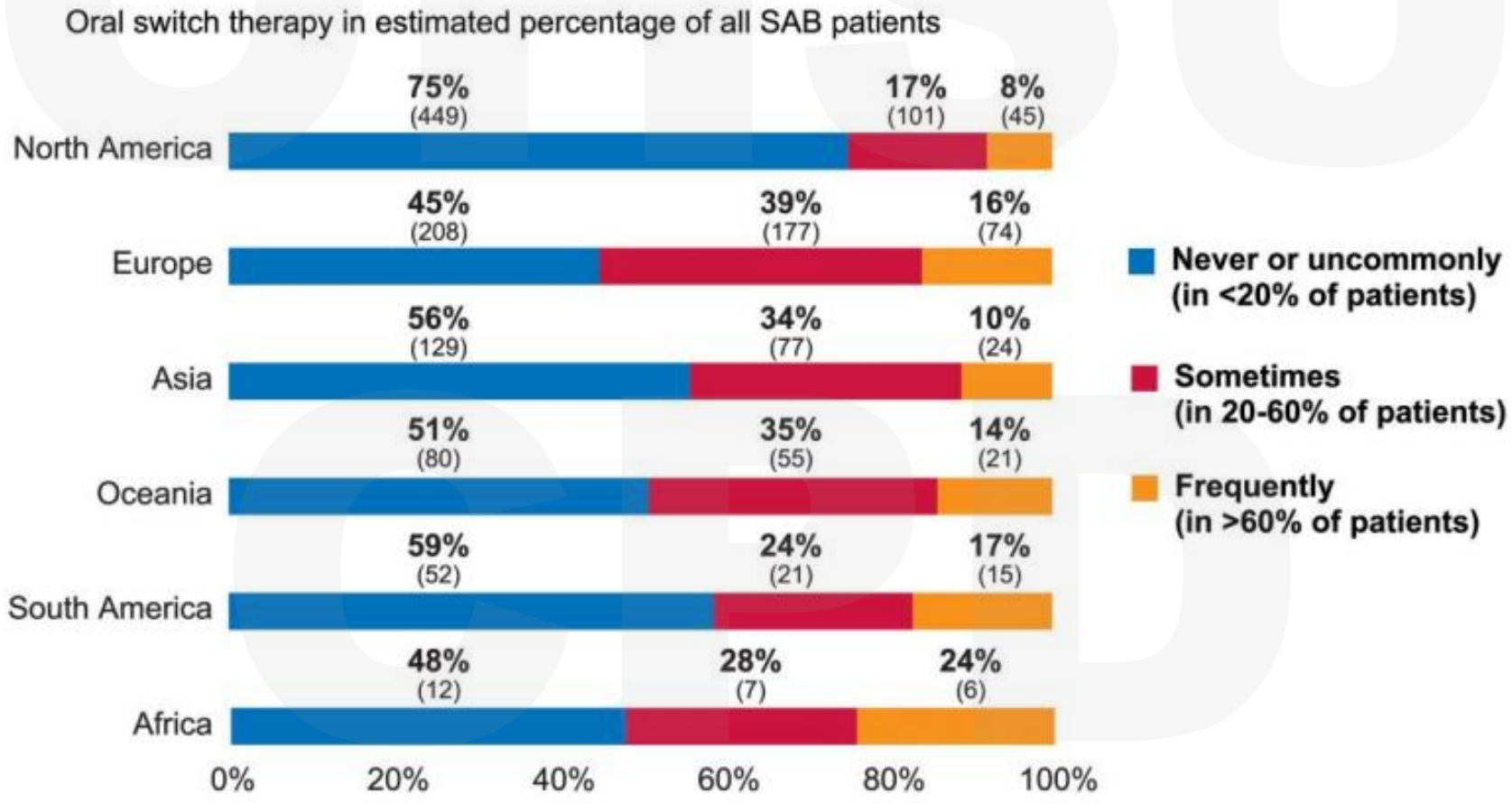
Sutton J, et al. *JAMA Netw Open* 2020.

Summary – approach to oral therapies of gram negative bacteremia

- Uncomplicated bacteremia with source control
- Not moderately to severely immunocompromised
- Clinical improvement within 72 hours of effective antibiotic treatment
- Transition to 1:1 orals
- Uncomplicated genitourinary infections – beta lactams may be a consideration
- Duration 7 days total

Staphylococcus aureus Bacteremia

Can we safely utilize oral antibiotics in the treatment of *Staph aureus* bacteremia?



Westgeest AC, et al. *Clin Infect Dis* 2023.

This is not a new concept

- Since 1975: 15 uncontrolled, observational studies, of oral treatment of IE
- >500 pts treated orally
- 12 series of <50 pts: high dose oral beta lactam, cipro + rif, or linezolid monotherapy = 77%-100% cure rates
- 3 controlled observational studies of IV to po stepdown
  - 66 pts switched after 18 days
  - 214 switched after 21 days
  - 171 patients treated with IV TMP-SMX (2 DS TID equivalent) + 600 mg IV clinda TID → 5 weeks of 2 DS TID TMP-SMX
- In all 3 of these studies patients did as well or better on orals

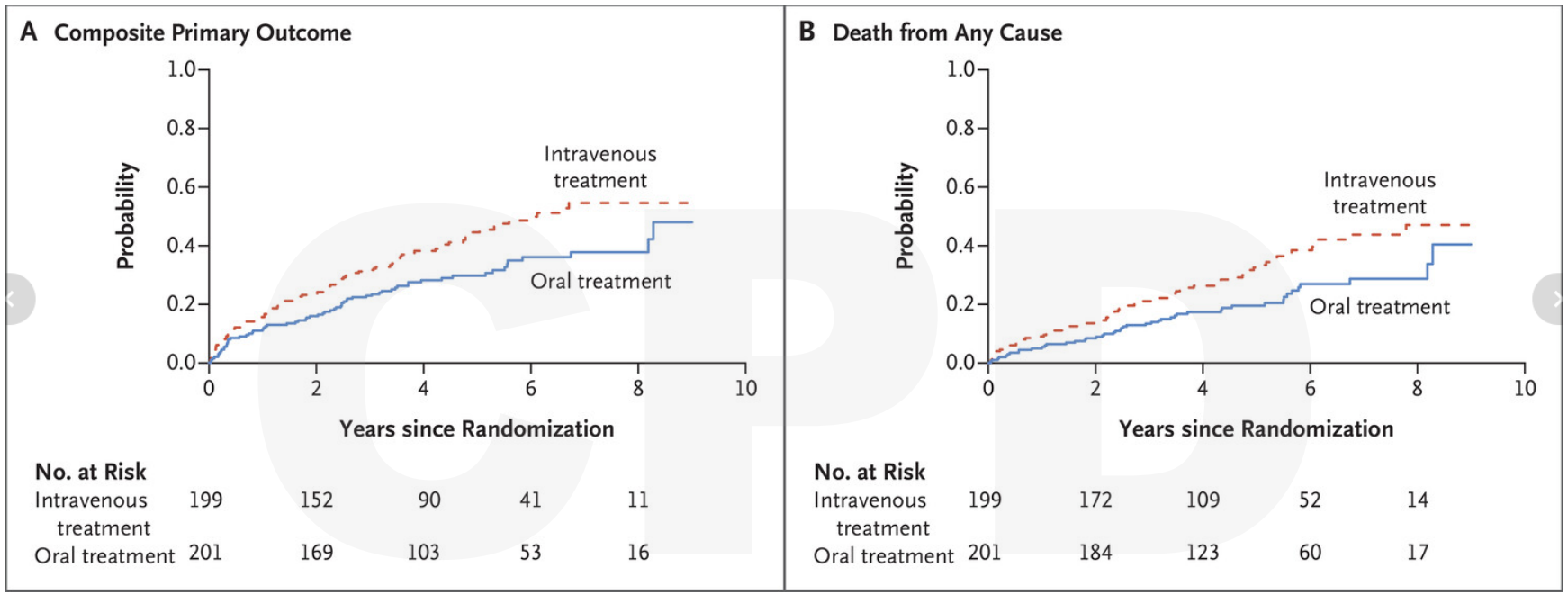
Spellberg B, et al. *JAMA Intern Med* 2020.

The NEW ENGLAND JOURNAL of MEDICINE

CORRESPONDENCE

Five-Year Outcomes of the Partial Oral Treatment of Endocarditis (POET) Trial

Published February 9, 2022 | N Engl J Med 2022;386:601-602 | DOI: 10.1056/NEJMc2114046 | VOL. 386 NO. 6



Pries-Heje MM et al. *N Engl J Med* 2022.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

Kasper Iversen, M.D., D.M.Sc., Nikolaj Ihlemann, M.D., Ph.D.,

Methicillin sensitive *Staphylococcus aureus* and coagulase-negative staphylococci

1) Dicloxacillin 1 g x 4 and fusidic acid 0.75 g x 2
2) Dicloxacillin 1 g x 4 and rifampicin 0.6 g x 2
3) Linezolid 0.6 g x 2 and fucidic acid 0.75g x 2
4) Linezolid 0.6 g x 2 and rifampicin 0.6 g x 2

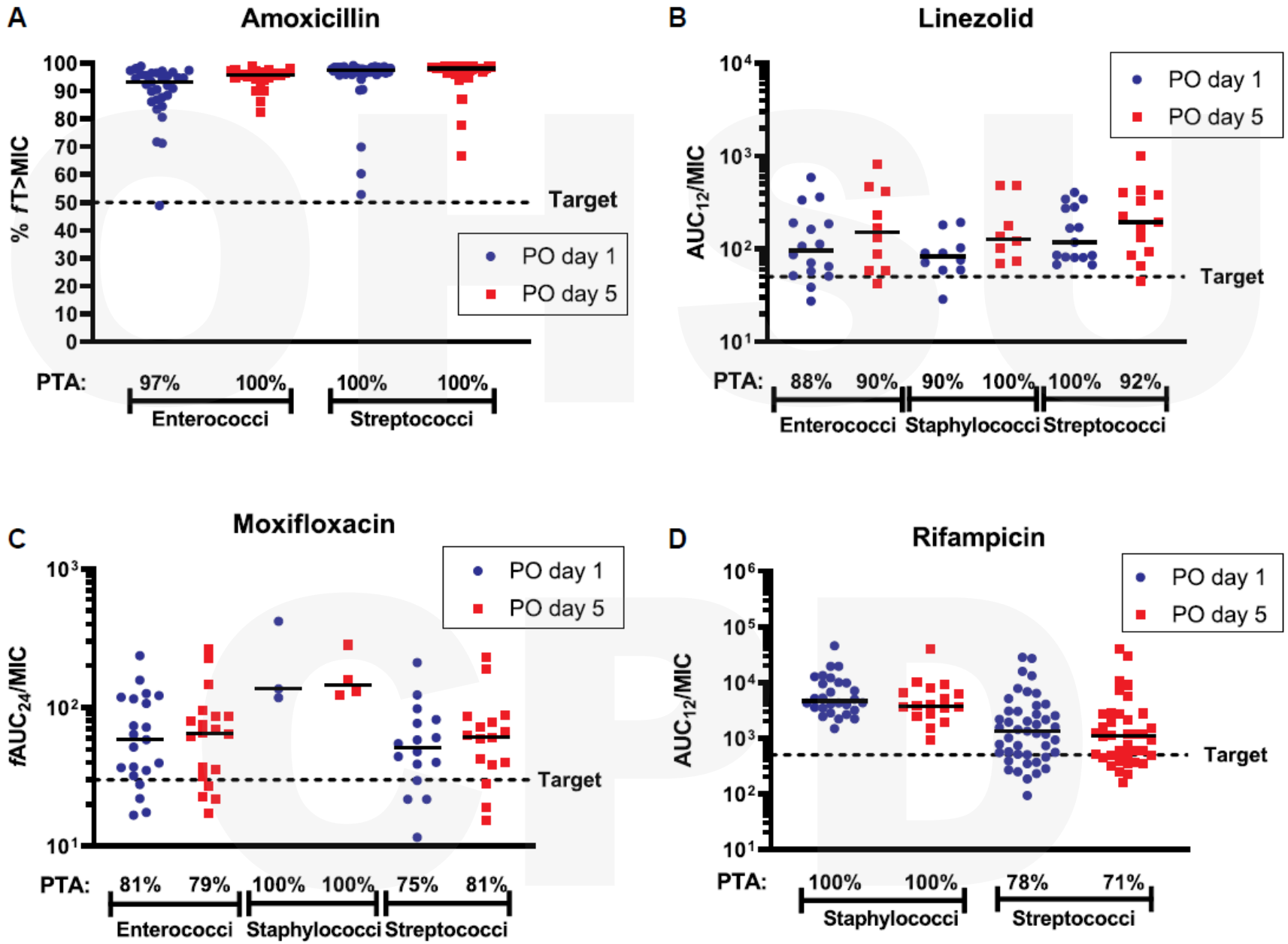
Iversen K, et al. *N Engl J Med* 2019.

Table S10

Antibiotic regimens in the POET trial.

	Oral regimens	Frequency n (%)
Staphylococcus aureus	Dicloxacillin and rifampicin	15 (33)
	Amoxicillin and rifampicin	13 (29)
	Moxifloxacin and rifampicin	3 (7)
	Amoxicillin and fusidic acid	2 (4)
	Dicloxacillin and fusidic acid	2 (4)
Enterococcus faecalis	Amoxicillin and moxifloxacin	24 (47)
	Amoxicillin and linezolid	13 (25)
	Amoxicillin and rifampicin	6 (12)
	Moxifloxacin and linezolid	5 (10)
Streptococci	Amoxicillin and rifampicin	47 (52)
	Amoxicillin and moxifloxacin	12 (13)
	Rifampicin and linezolid	8 (9)
	Moxifloxacin and linezolid	8 (9)
	Amoxicillin and linezolid	7 (8)

https://www.nejm.org/doi/suppl/10.1056/NEJMoa1808312/suppl_file/nejmoa1808312_appendix.pdf



Bock M, et al. *Clin Infect Dis* 2023.

Clinical Infectious Diseases

MAJOR ARTICLE

IDSA Infectious Diseases Society of America

hivma hiv medicine association

OXFORD

Real-World Application of Oral Therapy for Infective Endocarditis: A Multicenter, Retrospective, Cohort Study

Sarah Freling,[1,2] Noah Wald-Dickler,[1,2] Josh Banerjee,[1] Catherine P. Canamar,[1] Soodtida Tangpraphaphorn,[1] Dara Bruce,[3] Kusha Davar,[1] Fernando Dominguez,[1] Daniel Norwitz,[3] Ganesh Krishnamurthi,[1,2] Lilian Fung,[1,2] Ashley Guanzon,[1,4] Emi Minejima,[1,4] Michael Spellberg,[1] Catherine Spellberg,[1] Rachel Baden,[1] Paul Holtom,[1,2] and Brad Spellberg[1]

- 257 IE patients – 46 transitioned to oral
- Primary outcome – clinical success at 90 days
- IV group – more aortic valve, older, more dialysis, more CVCs
- PO group – more MRSA
- No difference in primary outcome, fewer adverse events in PO arm

Freling S, et al. *Clin Infect Dis* 2023.

Summary – approach to oral therapies for *Staph aureus* bacteremia

It's **NOT** a contaminant

S. aureus bacteremia can be managed with oral antibiotics

HOWEVER… Highly selected patients

Highly selected antibiotics

The best studied regimens can be tricky

Streptococcal and Enterococcal Bacteremia

Oral antibiotics for uncomplicated Streptococcal bacteremia

- **Amoxicillin 1000 mg q8h**
- **Linezolid**

- Cephalexin **1000 mg q6h**
- Cefpodoxime **400 mg q12h**
- Clindamycin **600 mg q8h** (significant rates of GAS and GBS resistance)

- Fluoroquinolones

Summary – Approach to oral therapies for *Streptococcus* and *E. faecalis* bacteremia

- Transition to PO ok after clinical improvement and stability achieved
- For uncomplicated streptococcal bacteremia due to susceptible organisms*, ok to transition to amoxicillin 1000 mg q8h
- For uncomplicated *E. faecalis* bacteremia → amoxicillin 1000 mg q6h or linezolid
- For infective endocarditis, use combination regimens with 1:1 oral agents or amoxicillin 1000 mg q6h

**Strep pyogenes* and *Strep agalactiae* expected to be penicillin susceptible

Remember - Not all orals are created equal

- There is no magic in the IV, the magic is in the PK-PD
- Use regimens that have been studied
- Make sure to use correct doses and frequencies

Amoxicillin 1000 mg Q8h for Strep

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