

PRISMA HEALTHSM

Is It Time?

By Mark Call, MD

Just to Get the Juices Flowing!

- I am weightless, but you can see me. Put me in a bucket, and I'll make it lighter. What am I?
- You throw away the outside and cook the inside. Then you eat the outside and throw away the inside. What did you eat?
- What can run but never walks, has a mouth but never talks, has a head but never weeps, has a bed but never sleeps?
- The man who built it doesn't want it. The man who bought it doesn't want it. The man who's using it doesn't know he's using it. What is it?

I HAVE LIKE.....

**NO CONFLICTS OF
INTEREST**



My Goals for This Talk...



EIN Survey With the Following Questions

- How often do you transition from intravenous to oral antibiotic therapy for patients with IE?
 - Never
 - Rarely ($\leq 10\%$ of cases)
 - Occasionally (11-25% of cases)
 - Frequently (26-50% of cases)
 - Very frequently ($> 50\%$ of cases)
- Please select the THREE factors below that most influence your decision whether to transition to oral therapy for IE?
 - Availability of oral antibiotic options with appropriate spectrum
 - Pathogen
 - Clearance of bloodstream infection
 - Adherence potential to oral therapy with follow-up
 - Desire to avoid prolonged intravascular use
 - Prosthetic valve or prosthetic valve material
 - Imaging evidence of stable or improving valvular infection
- For which pathogens do you feel comfortable transitioning to oral therapy?
 - N/A, do not transition to oral therapy
 - Streptococcus spp.
 - Gram-negative bacilli
 - HACEK (Haemophilus, Aggregatibacter Cardiobacterium, Eikenella, Kingella)
 - MSSA 124
 - Coagulase-negative staphylococci
 - Enterococcus spp.
 - MRSA

EIN Survey Continued

- The POET trial used transitional oral antibiotic therapy with two antibiotics (combination therapy). In your practice, which best describes your usual approach?
 - I do not use transitional oral antibiotic therapy
 - I always use two oral antibiotics until completion of therapy
 - I typically use a single oral antibiotic unless the pathogen specifically requires two antibiotics (e.g. *C. burnetii*, *Bartonella* IE)
- What are the primary issues that prevent you from prescribing transitional oral therapy for IE?
 - Fear of treatment failure or recurrence
 - Concerns about patient adherence
 - Lack of sufficient evidence
 - Patient comorbidities (e.g. gastrointestinal absorption issues)
 - Medicolegal issues
 - Institutional guidelines or restrictions
 - None, I use transitional oral therapy regularly
- Which choice best describes your approach to transitioning from IV to oral therapy in people who inject drugs (PWID) with IE?
 - I never consider an oral switch
 - I rarely consider an oral switch
 - I occasionally consider an oral switch
 - I often consider an oral switch
 - I always consider an oral switch

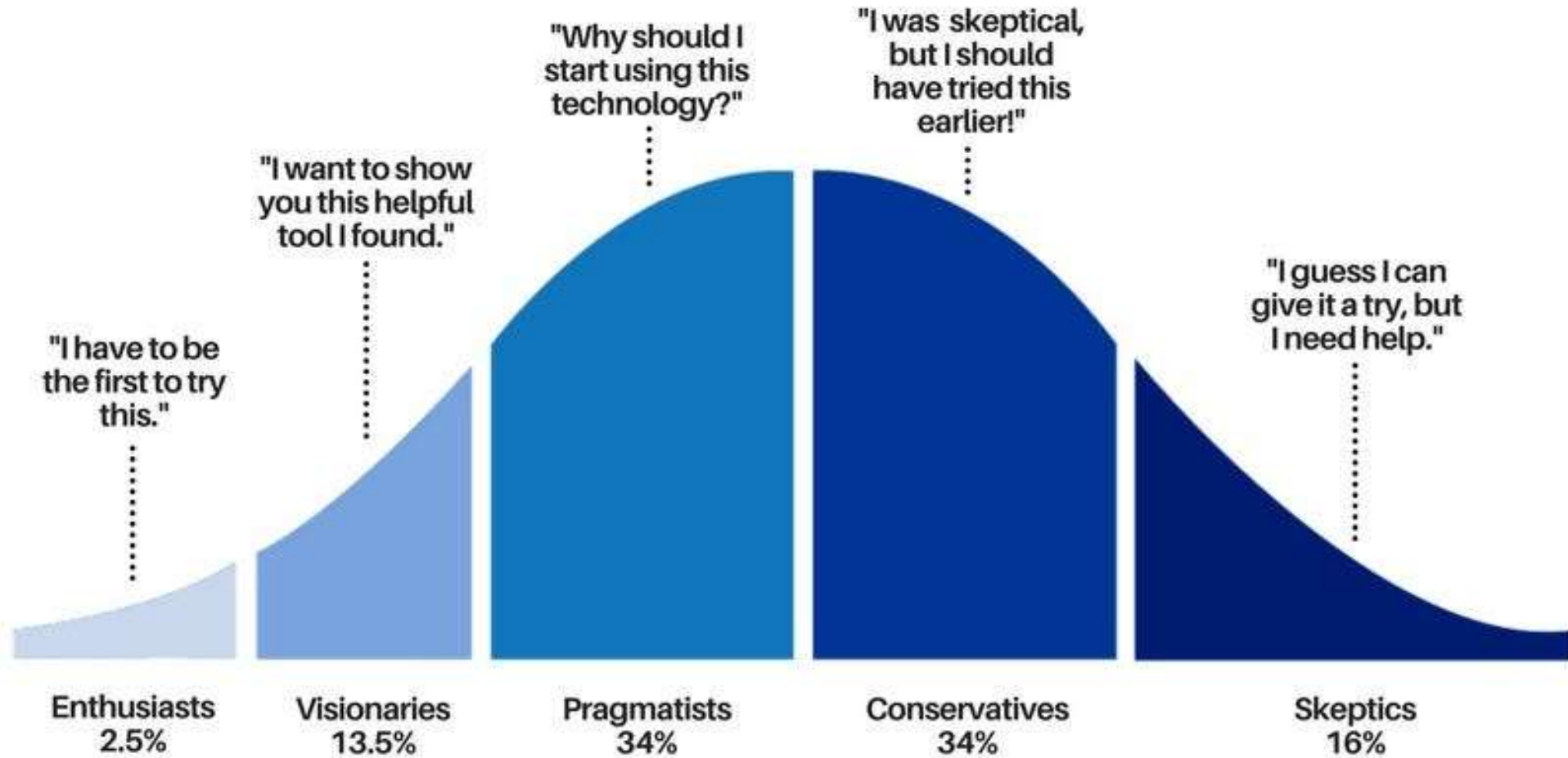
EIN Survey Cont.

- How strongly do current guidelines (e.g. AHA, ESC) influence your decision to consider transitional oral therapy for infective endocarditis?
 - Not at all
 - Slightly
 - Moderately
 - Strongly
 - Very strongly
- What would increase the likelihood of incorporating transitional oral therapy into your practice?
 - N/A, will not use transitional oral therapy
 - Clearer guidelines or consensus statements
 - More prospective clinical trial data
 - Improved methods to monitor patient adherence
 - Access to oral antibiotic regimens with appropriate coverage
 - Institutional protocols or support

Thoughts?



The Adoption Curve



First Up



POET Trial Overview

- Randomized, non-inferiority, multi-center exclusively in Denmark
- All patients received at least **10 days of IV** antibiotics
- **Primary outcome:**
 - A composite of all-cause mortality,
 - Unplanned cardiac surgery,
 - Embolic events, or
 - Relapse of bacteremia with the primary pathogen,
 - Randomization - 6 mo after completion of antibiotics
- **Eligible patients:**
 - > 18 yo
 - Left-sided IE due to:
 - *Streptococcus*,
 - *E. Faecalis*,
 - *Staphylococcus Aureus*, or
 - CoNS.
 - Included patients with **cardiac devices** and those who **underwent valve surgery** (had to be on IV for at least 7 days post-op)

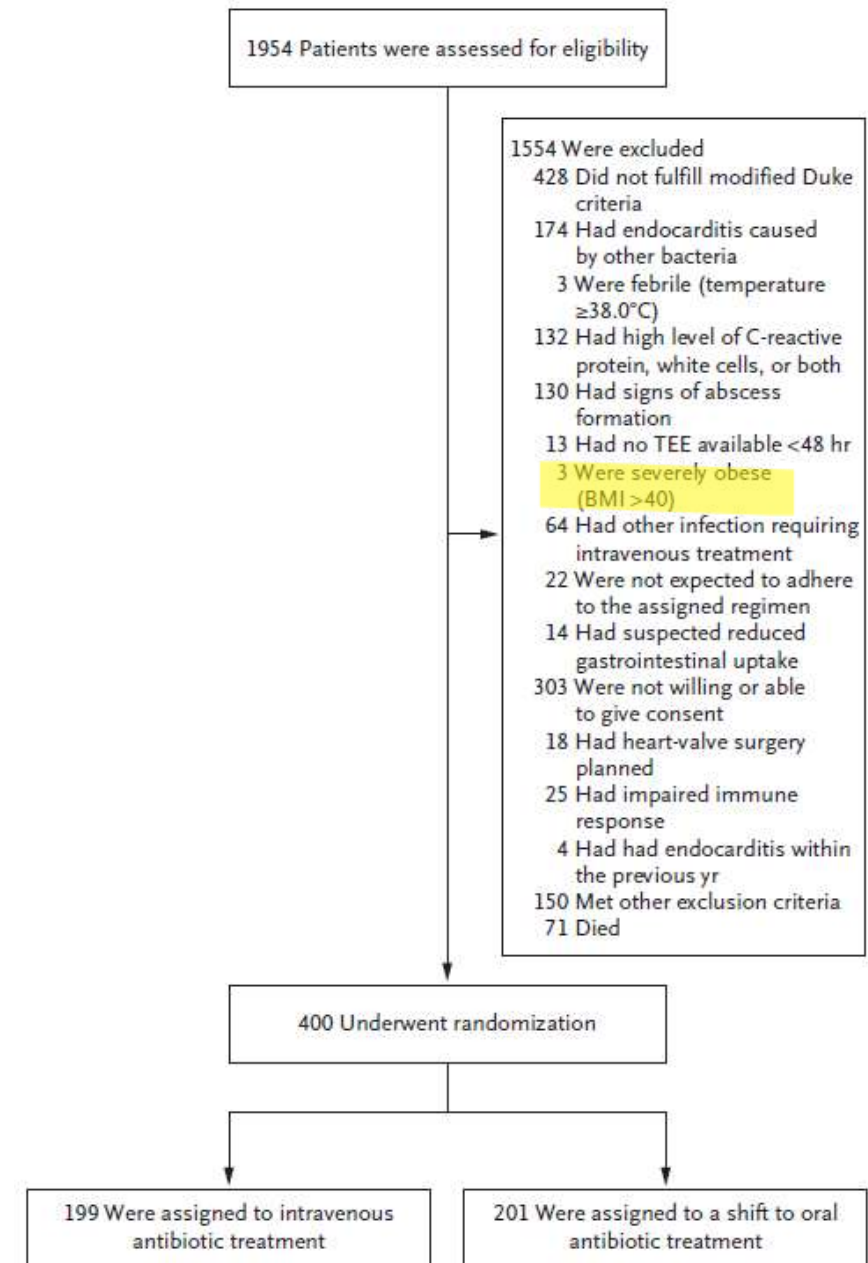
POET Follow Up Protocol

- **Oral:** seen 2-3x/wk (while on treatment)
- Within 1-3 days before the completion of the assigned antibiotic treatment, **TEE was performed** to confirm
- **All patients:** 1 week and at 1, 3, and 6 months after completion of antibiotic treatment.

	Oral regimens	Frequency n (%)
<i>Staphylococcus aureus</i>	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)
	Fusidic acid and linezolid	2 (4)
	Rifampicin and linezolid	2 (4)
	Penicillin and rifampicin	1 (2)
	Amoxicillin and clindamycin	1 (2)
	Ampicillin and rifampicin	1 (2)
	Moxifloxacin and fusidic acid	1 (2)
	Moxifloxacin and linezolid	1 (2)
	Linezolid and clindamycin	1 (2)
<i>Enterococcus faecalis</i>	Amoxicillin and moxifloxacin	24 (47)
	Amoxicillin and linezolid	13 (25)
	Amoxicillin and rifampicin	6 (12)
	Moxifloxacin and linezolid	5 (10)
	Amoxicillin and ciprofloxacin	2 (4)
	Amoxicillin	1 (2)
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)
	Penicillin	3 (3)
	Ampicillin and moxifloxacin	1 (1)
	Ampicillin and rifampicin	1 (1)
	Dicloxacillin and moxifloxacin	1 (1)
	Moxifloxacin and clindamycin	1 (1)
	Moxifloxacin and vancomycin	1 (1)
Coagulase negative staphylococci	Fusidic acid and linezolid	5 (38)
	Rifampicin and linezolid	4 (31)
	Amoxicillin and linezolid	1 (8)
	Dicloxacillin and rifampicin	1(8)
	Moxifloxacin and linezolid	1(8)
	Rifampicin and Fusidic acid	1(8)

POET Trial Continued

- Oral regimens consisted of:
 - **two antibiotics** from **different drug classes** with **different antimicrobial mechanisms of action** and **different metabolism processes**
- Blood samples for the measurement of **plasma levels** of orally administered antibiotics were obtained.
- The most frequent **reasons for exclusion** were an unconfirmed diagnosis (22%), an unwillingness or inability to give informed consent (16%), or an infection that was caused by other bacteria (9%)
- The two groups were **well-balanced** and 35% had at least one major coexisting condition.



POET Cont.

- Median time from the dx. to randomization was **17d**
- Oral group, 160 patients (**80%**) were partially or completely treated as outpatients.
- After randomization the median LOS was **19 days** in the IV group and **3 days** in the orally treated group

Table 2. Distribution of the Four Components of the Primary Composite Outcome.*

Component	Intravenous Treatment (N=199)	Oral Treatment (N=201)	Difference	Hazard Ratio (95% CI)
	number (percent)		percentage points (95% CI)	
All-cause mortality	13 (6.5)	7 (3.5)	3.0 (−1.4 to 7.7)	0.53 (0.21 to 1.32)
Unplanned cardiac surgery	6 (3.0)	6 (3.0)	0 (−3.3 to 3.4)	0.99 (0.32 to 3.07)
Embolic event	3 (1.5)	3 (1.5)	0 (−2.4 to 2.4)	0.97 (0.20 to 4.82)
Relapse of the positive blood culture†	5 (2.5)	5 (2.5)	0 (−3.1 to 3.1)	0.97 (0.28 to 3.33)

Table 1. Characteristics of the Patients at Baseline.*

Characteristic	Intravenous Treatment (N=199)	Oral Treatment (N=201)
Mean age — yr	67.3±12.0	67.6±12.6
Female sex — no. (%)	50 (25.1)	42 (20.9)
Body temperature — °C	36.9±0.45	37.0±0.44
Coexisting condition or risk factor — no. (%)		
Diabetes	36 (18.1)	31 (15.4)
Renal failure	25 (12.6)	21 (10.4)
Dialysis	13 (6.5)	15 (7.5)
COPD	17 (8.5)	9 (4.5)
Liver disease	7 (3.5)	6 (3.0)
Cancer	14 (7.0)	18 (9.0)
Intravenous drug use	3 (1.5)	2 (1.0)
Pathogen — no. (%)†		
Streptococcus	104 (52.3)	92 (45.8)
Enterococcus faecalis	46 (23.1)	51 (25.4)
Staphylococcus aureus‡	40 (20.1)	47 (23.4)
Coagulase-negative staphylococci	10 (5.0)	13 (6.5)
Laboratory results at randomization		
Hemoglobin — mmol/liter	6.3±1.1	6.5±1.0
Leukocytes — ×10 ⁹ /liter	7.6±3.6	7.2±2.6
C-reactive protein — mg/liter	24.3±18.4	19.9±16.7
Creatinine — μmol/liter	124±112	141±164
Preexisting prosthesis, implant, or cardiac disease — no. (%)		
Prosthetic heart valve	53 (26.6)	54 (26.9)
Pacemaker	15 (7.5)	20 (10.0)
Other known valve disease	82 (41.2)	90 (44.8)
Cardiac involvement at randomization — no. (%)§		
Mitral-valve endocarditis	65 (32.7)	72 (35.8)
Aortic-valve endocarditis	109 (54.8)	109 (54.2)
Mitral-valve and aortic-valve endocarditis	23 (11.6)	20 (10.0)
Endocarditis in other locations§	2 (1.0)	0
Pacemaker endocarditis	6 (3.0)	8 (4.0)
Vegetation size >9 mm	7 (3.5)	11 (5.5)
Moderate or severe valve regurgitation	19 (9.5)	23 (11.4)
Valve surgery during current disease course	75 (37.7)	77 (38.3)

POET Cont.

- “It should be noted that the primary outcome seemed similar across the four different bacterial types. **However, the trial was not powered to assess the primary outcome in any of the prespecified subgroups.**”

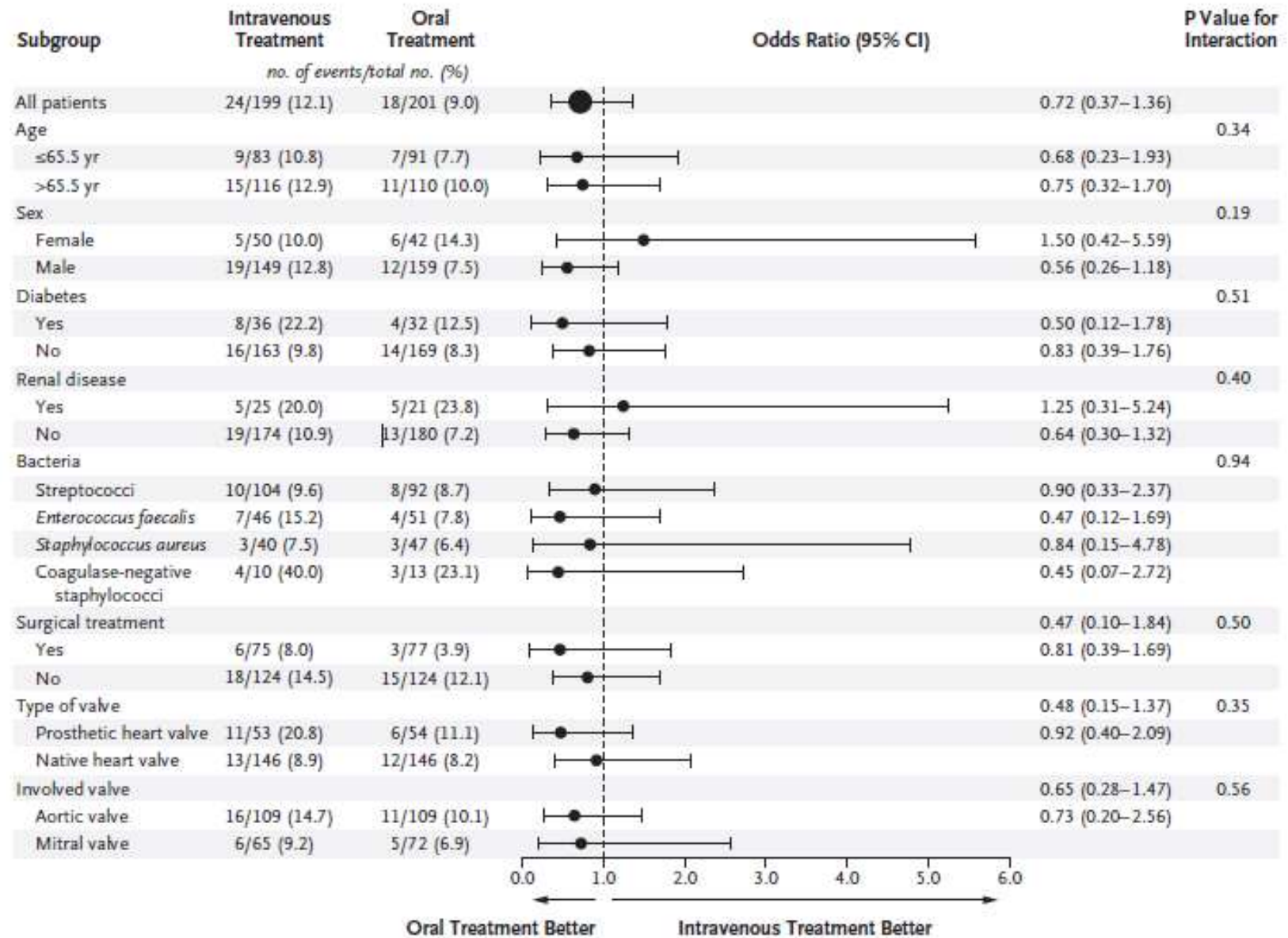
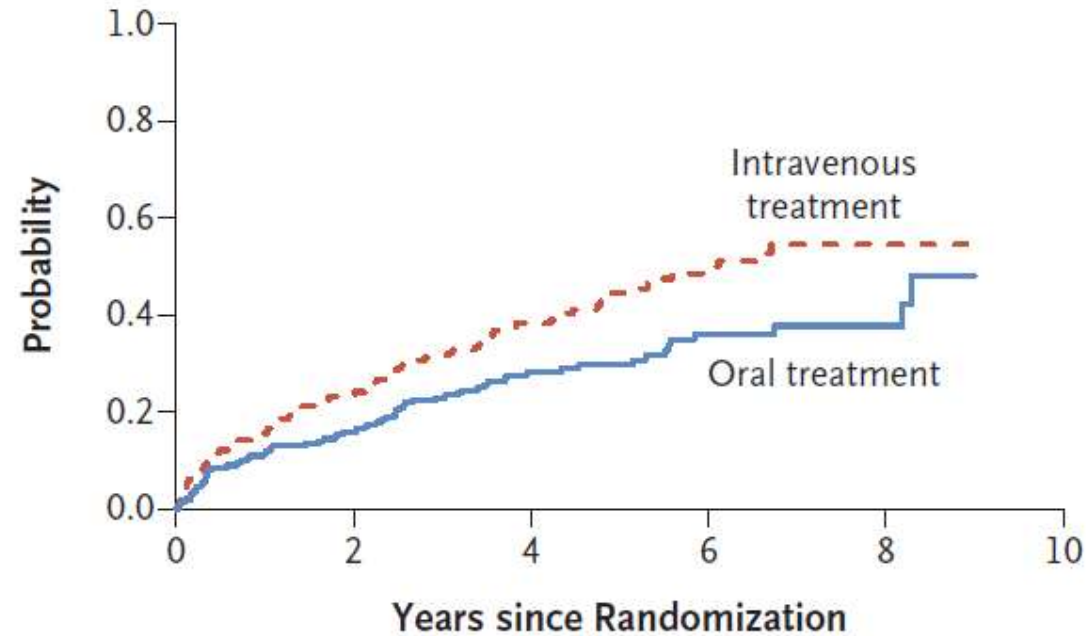


Figure 3. Rates of the Primary Outcome in Prespecified Subgroups.

Five Year Outcomes of the POET Trial

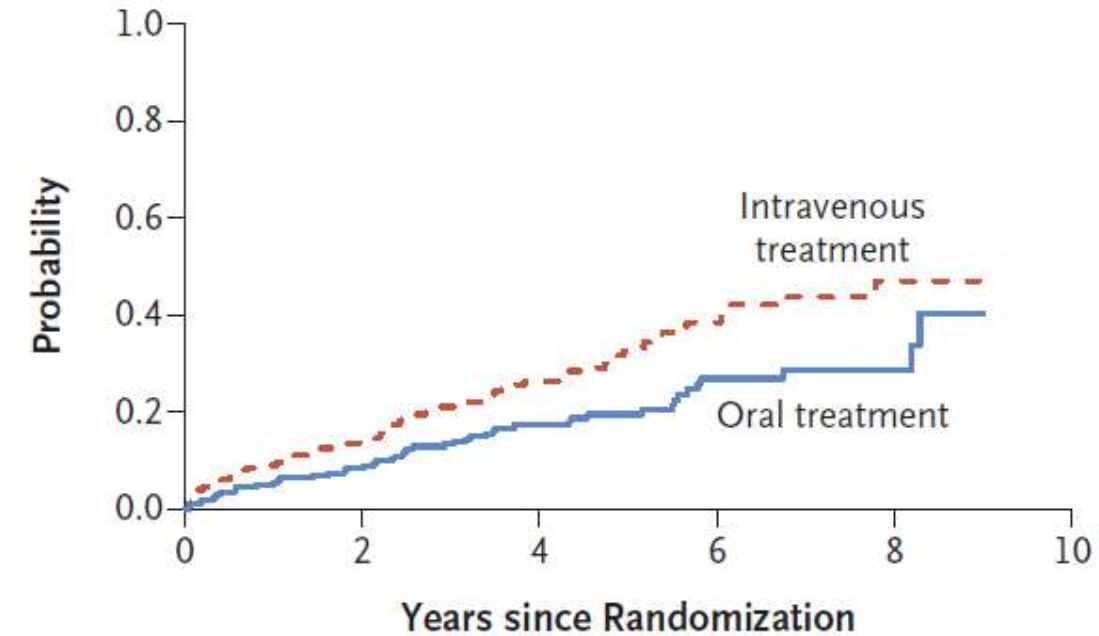
A Composite Primary Outcome



No. at Risk

Intravenous treatment	199	152	90	41	11
Oral treatment	201	169	103	53	16

B Death from Any Cause



No. at Risk

Intravenous treatment	199	172	109	52	14
Oral treatment	201	184	123	60	17

Pries-Heje et. al. N Engl J Med 2022;386: 601–602

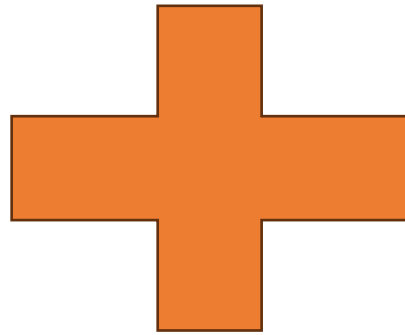
A Penny
For Your
Thoughts



Next UP...



Poe



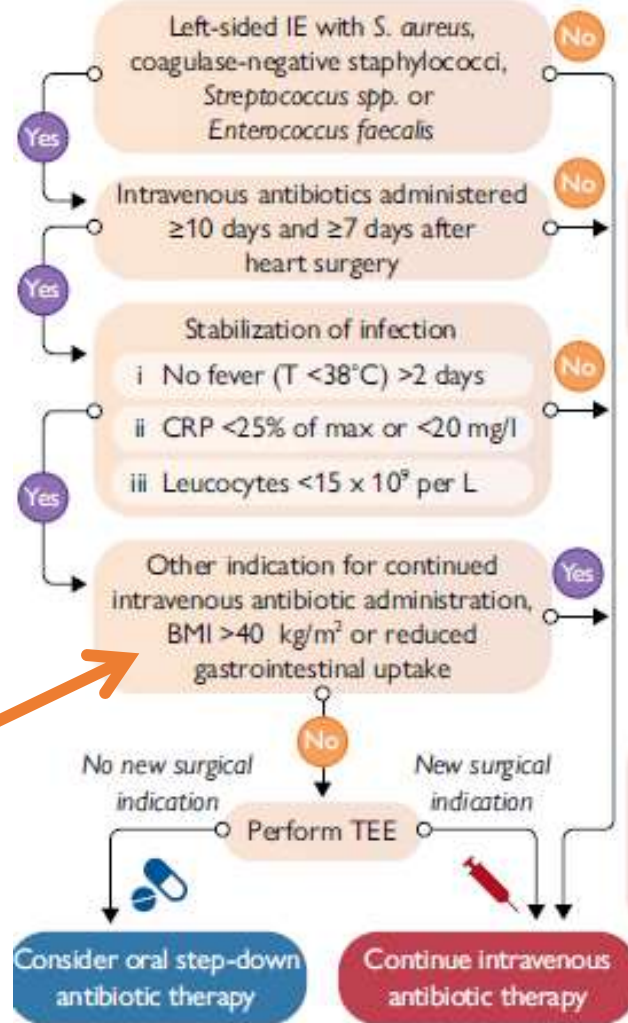
Try

Clinical implementation of partial oral treatment in infective endocarditis: the Danish **POETry** study

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Stabilization criteria

POET



Median length of stay

Oral step-down = 24 days (IQR 17–36)
 Intravenous = 43 days (IQR 32–51)
 ($p < 0.001$)

Composite primary outcome

- Symptomatic embolic event
- Unplanned cardiac surgery
- Relapse of bacteraemia
- All-cause mortality

1017 Patients with IE

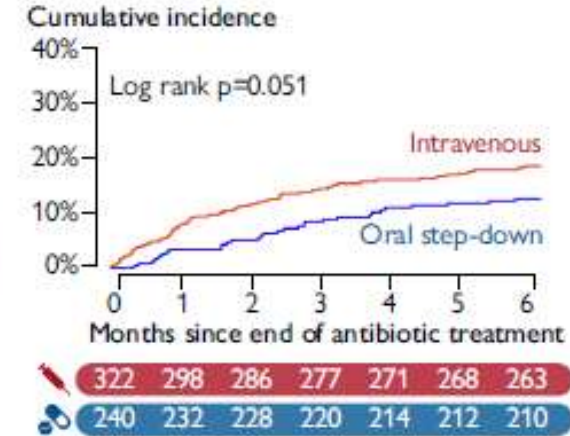
455 Patients excluded due to ineligibility or death

562 Patients considered possible candidates for POET-treatment

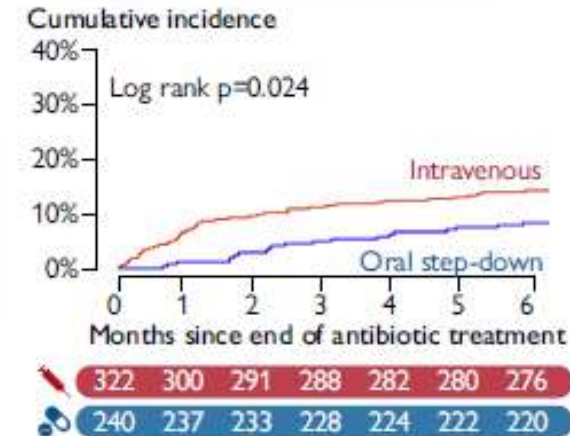
240 Patients received oral step-down antibiotic therapy

322 Patients received traditional intravenous antibiotic therapy

A Primary outcome

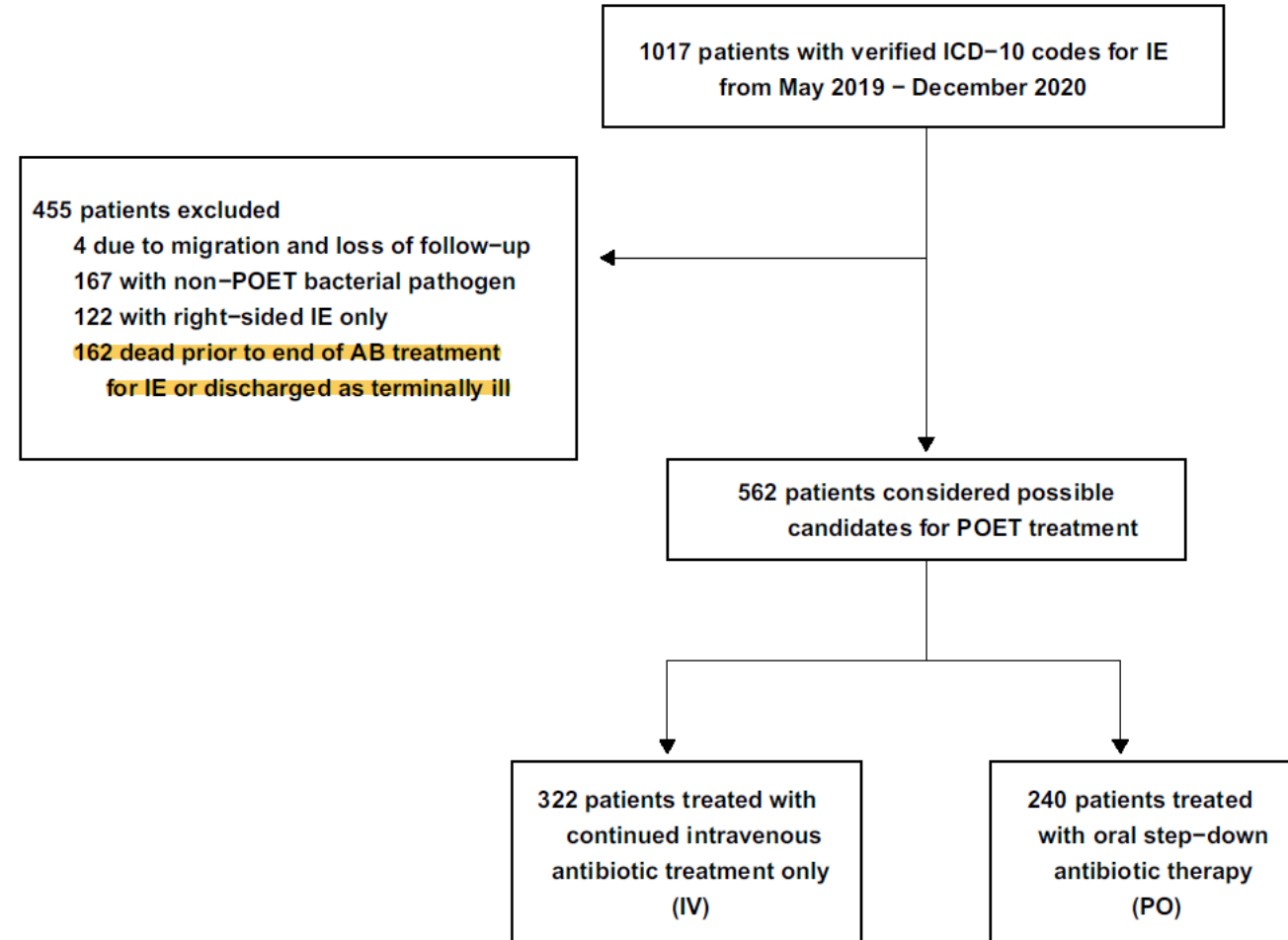


B All-cause mortality



POETry Findings

- Retrospective national observational cohort study.
- **Exclusion Criteria:**
 - Right-sided only,
 - Different Bacteria,
 - Lost to f/u,
 - Excluded from the primary analysis if they died or went comfort care before completing antibiotics.
- **45%** were excluded
 - **16% died before** treatment was finalized or went comfort care
 - Exclusion due to mortality occurred most due to **Staph Aureus**.



POETry Cont.

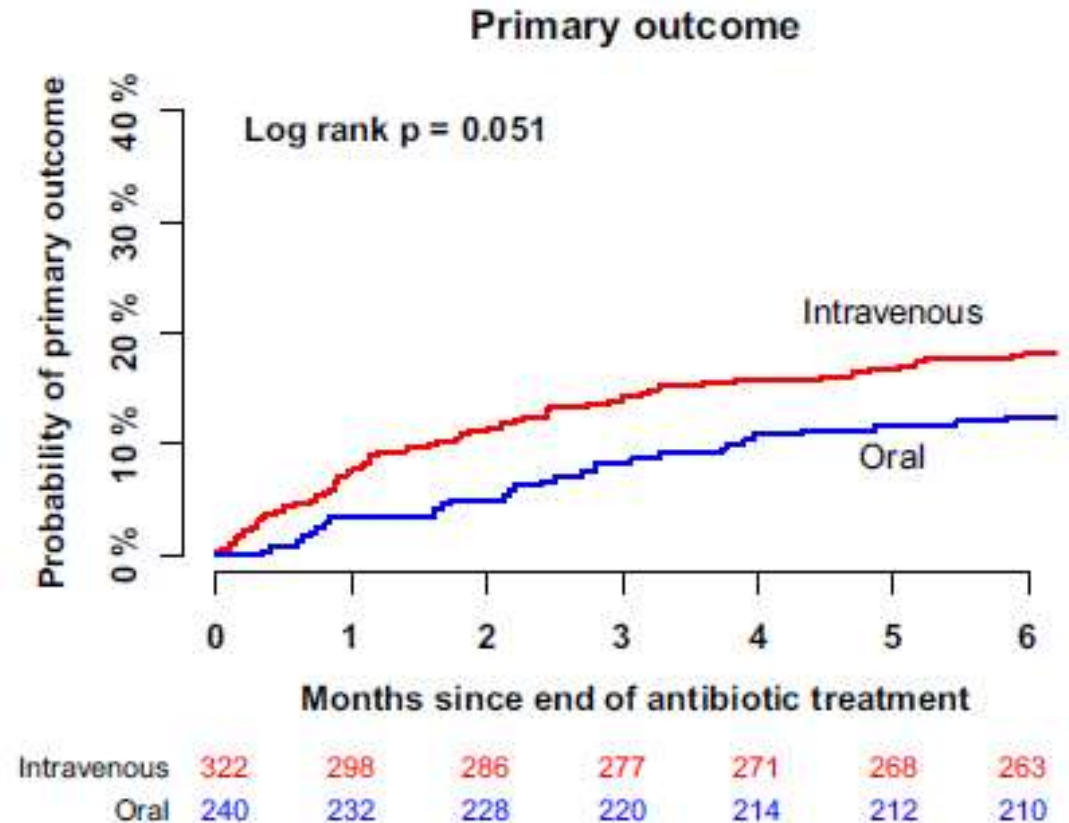
- **PVIE in 28%** and **CIED infected in 10%** of all patients
- Switched to po at a median of **16 days**
- Oral tx group:
 - **28% failed to meet one criteria for stabilization**
 - **TEE** was the criteria missed most often (**62%**)
 - Occurrence of **primary outcome** in this group (**22% vs 9%**) with $P = 0.005$
 - Only 1 antibiotic in **5%**
 - Event occurrence of **33% vs 11%** ($P = 0.07$)
- In 138 out of 322 (**43%**) remaining on IV, **no apparent reason** was met for not switching to po.

Table 2 Clinical characteristics of patients

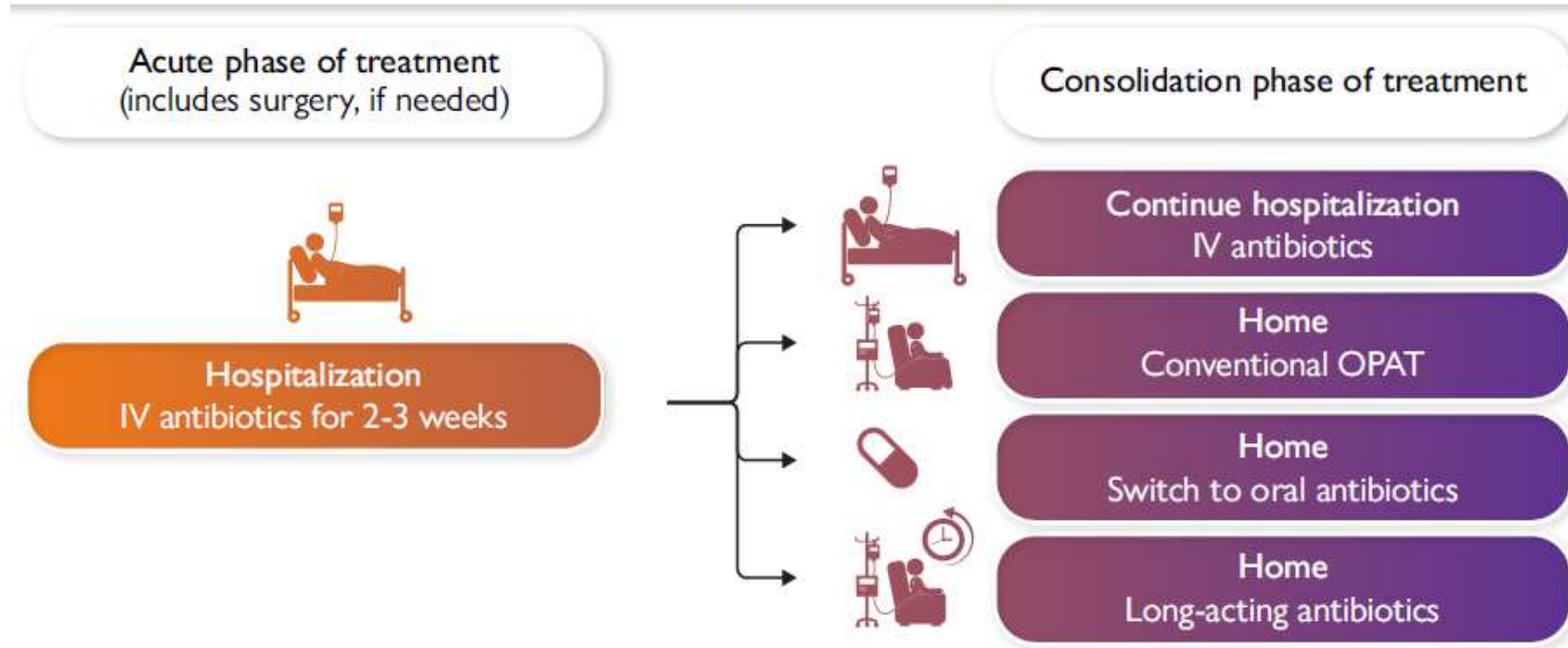
	PO, n = 240	IV, n = 322	P-value
Characteristics			
Age, years—median (IQR)	73 (65.0, 80.0)	74 (66.0, 80.0)	.52
Male, n (%)	166 (69.2%)	228 (70.8%)	.67
Comorbidities—n (%)			
Diabetes	53 (22.1%)	78 (24.2%)	.55
Chronic kidney disease ^a	67 (27.9%)	92 (28.6%)	.94
Chronic dialysis	10 (6.5%)	23 (11.8%)	.09
Liver disease	19 (7.9%)	20 (6.2%)	.43
COPD	57 (23.8%)	74 (23.0%)	.83
Intravenous drug use	7 (2.9%)	3 (0.9%)	.11
Cancer	34 (14.2%)	45 (14.0%)	.95
Pre-existing prosthesis or intra-cardiac implant—n (%)			
Prosthetic heart valve	81 (33.8%)	92 (28.6%)	.19
Pacemaker/ICD	23 (9.6%)	49 (15.3%)	.05
Pathogen—n (%)			
<i>Staphylococcus aureus</i>	71 (29.6%)	131 (40.7%)	.01
<i>Enterococcus faecalis</i>	45 (18.8%)	49 (15.2%)	.27
<i>Streptococcus</i> spp.	106 (44.2%)	126 (39.1%)	.23
Coagulase-negative staphylococci	19 (7.9%)	19 (5.9%)	.35
Cardiac involvement—n (%)			
Definite endocarditis ^b	199 (82.9%)	287 (89.1%)	.01
Prosthetic heart valve endocarditis	70 (29.2%)	88 (27.3%)	.63
Cardiac device-related endocarditis	13 (5.4%)	24 (7.5%)	.34
Intra-cardiac abscess	14 (5.8%)	38 (11.8%)	.02
Heart valve surgery	39 (16.2%)	84 (26.1%)	.01
Affected valve			.14
Aortic	126 (52.5%)	174 (54.0%)	
Mitral	96 (40.0%)	110 (34.2%)	
Both	18 (7.5%)	38 (11.8%)	

POETry, Final Thoughts...

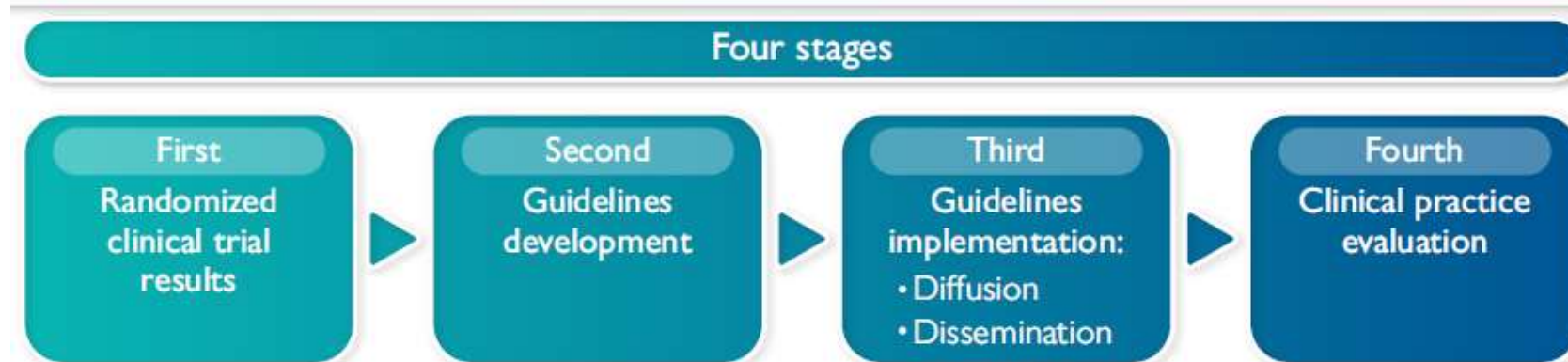
- Pt's in this trial were **older**, had a higher prevalence of pre-existing conditions (**55% vs 35%**), and a greater proportion evaluated were included in the study (**55% vs 20%**).
- **Staph aureus** noted in **36%** of this study vs 22% in POET
- The incidence of the primary outcome in patients who fulfilled stabilization criteria at the time of switch to PO treatment was the same as seen in the POET RCT (**9% vs. 11%**).
- Prevalence of patients undergoing **surgery (22%)** was lower c/w **POET (38%)** but was in accordance with Denmark rates.
 - **Abscess formation** accounted for a third of surgeries in POETry and most of these patients were left on IV.
 - **No events in the 14 pts** with intra-cardiac abscess tx'd w/ po.



Current options for completing antimicrobial treatment in most cases of IE due to gram-positive microorganisms



The evidence-based medicine process



Long-acting Antibiotics?

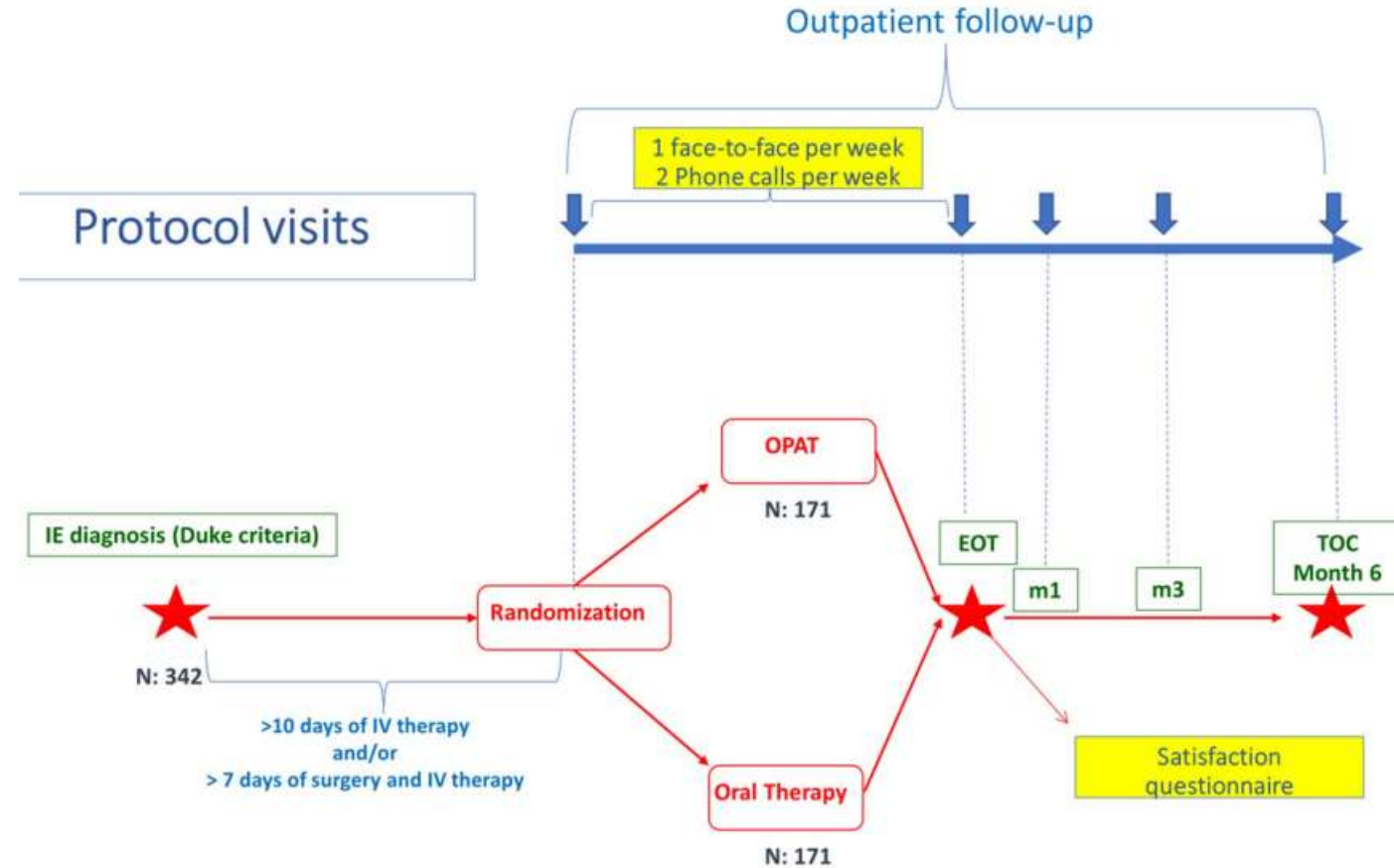
- Just prior to POET RCT publication, an Austrian study reporting the experience of using i.v. ***dalbavancin*** to treat 27 patients with Gram-positive IE, achieving a cure in 25 cases
 - *Tobudic et.al. Clin Infect Dis 2018;67:795–798*
- Gram-positive IE treated with dalbavancin as sequential therapy has been published in nine observational studies, with an overall clinical cure rate of **90%**
 - CoNS in 49%, followed by Staph aureus
 - “Further studies are needed.”
 - *Fazili et.al. Int J Antimicrob Agents 2023;61:106749*
 - *Leanza et.al. Infection 2025 Feb;53(1):15-23*

OraPAT-IEGAMES Study *Cuervo et.al. Inf Dis Ther (2025) 14:643–655*

- Builds on POET by focusing on **outpatient strategies**
- Non-inferiority, multicenter, randomized, open-label study in **Spain**
- Minimum of **10 days of IV** followed by randomization
- **Primary end-point** is a composite of all-cause mortality, unplanned cardiac surgery, relapse of positive blood cultures and/or unplanned hospital admission
- Followed for **6 mo** after completion of therapy
- Will not be powered to demonstrate differences between various subgroups of IE (e.g., native valve IE, prosthetic valve IE, specific micro-organisms, etc.)
- The **GAMES group** (**G**rupo de **A**poyo al **M**anejo de la **E**ndocarditis en **E**spaña), has published on expansion of OPAT protocols with IE

OraPAT-IEGAMES Continued

- **Secondary objectives:**
 - Quality of life
 - Costs of interventions through a pharmacoeconomic sub-study
 - Complications related to parenteral and oral administration of antibiotics
 - Such as antibiotics or catheter-related adverse events and superinfections.



OPAT Considerations

- Not adverse event free:
 - At least one IV access complication requiring intervention in **9%**
 - Significant event occurred in **14.5%**
 - Mean time for the first complication is **16.1 days**
 - **Overall complication rate was 30%**
 - Occlusion, accidental removal, infection, and thrombosis
 - *Laue et.al. Clin. Ther. 2011, 33, 1792–1796*
 - *Amodio-Groton et.al. Ann. Pharmacother. 1996, 30, 596–602.*

So, What About Bacteremia?



Staphylococcus aureus Treatment

Population



Hospitalized adult patients with **low-risk *S. aureus* bloodstream infection (SAB)**

Low-risk (ALL):

- (-) FUBC after 24-96 hr
- No s/sx metastatic infection
- IV catheters removed by 72 hr
- No prosthetic heart valve
- Not severely immunosuppressed

Study Design



- Randomized
- Open-label
- Non-inferiority

213

Patients

Inclusion criteria: Aged 18 or older; blood culture positive for *S. Aureus*, 5-7 days of appropriate IV antimicrobial therapy, and absence of persistent bacteremia. **Exclusion criteria:** Complicated *S. Aureus* bloodstream infection, non-removable foreign devices or severe comorbidity.



**Oral switch therapy
(n = 108)**

VS.



**Intravenous standard therapy
(n = 105)**

Primary Outcome

13

Occurrence of any complication related to *S. Aureus* bloodstream infection within 90 days %
Difference: 0.7, CI: -7.8 to 9.1 (P = 0.013)

12

Secondary Outcome

34

Adverse event in safety population %
(P = 0.29)

26

tic

Outcome

- 90-d SAB-Related Complication (composite):**
- Relapsing bacteremia
 - Deep-seated SA infection
 - Attributable mortality

Outcomes

- Length of stay
- Survival
- Complications of IV therapy
- *Clostridioides difficile*-associated diarrhea



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[ov/ct2/show/NCT01792804](https://clinicaltrials.gov/ct2/show/NCT01792804)

Linezolid for SAB (For Dr. Enwezor!)

- Listed as the **1st choice alternative** for MRSA bacteremia in by the UK Guidelines
- Non-inferior to *vanc* or *oxacillin* in gram-positive, mostly staph, CRBSI in terms of clinical or microbiological failure and mortality.
 - Wilcox et.al. Clin. Infect. Dis. **2009**, 48, 203–212
- Another trial found oral step-down *linezolid* (**after 5-7 days IV**) demonstrated similar clinical and safety outcomes compared with SPT for MRSA-BSI, except linezolid was associated with **fewer AEs requiring re-hospitalization**.
 - SPT group (161) were sicker overall:
 - Complicated bacteremia (72% vs. 41%; $P < 0.0001$) and
 - Metastatic foci (45% vs. 20%; $P = 0.001$).
 - When accounting for disease severity, linezolid use was not independently associated with 90-day IRR (adjOR, 1.0, 95% CI 0.24-4.3; $P = 0.986$)
 - Yeager et.al. Int. J. Antimicrob. Agents **2021**, 57



Quinolones for SAB (Again for Dr. Enwezor)

- Not all quinolones are made alike.
- **Moxifloxacin** seems to be the most potent “anti-staphylococcal fluoroquinolone”.
 - An older PD model has showed that the equivalent daily dose of 400 mg of *moxifloxacin* against *S. aureus* is 5000 mg of *levofloxacin*
 - *Firsov et.al. JAC. 2000, 46, 725-732*
- The MIC breakpoint for killing and resistance suppression for moxifloxacin 400 mg qday should be = **0.06 mg/L**
 - High-dose *moxifloxacin* (800 mg/day) can increase this breakpoint to = 0.125 mg/L
- Moxifloxacin has also been effectively used in other **biofilm-associated infections** caused by *S. aureus* like orthopedic implant-related infections, either as monotherapy or in combination with rifampicin.
 - **Rifampicin lowers moxifloxacin** serum levels by ~30%
 - Relapses in such infections were **not attributed to on-treatment moxifloxacin resistance**, as opposed to when ciprofloxacin had been previously used as monotherapy



What About SAB and Foreign Bodies?

- Two post-hoc analyses of the INSTINCT cohort looking at the addition of rifampin in patients with **uninfected foreign bodies**.
 - *Rieg et.al. Clin. Micro. Inf. 2017, 23, 401-406*
 - *Rieg et.al. JAC. 2020, 75, 2282-2290*
- Observed that **68%** of late complications were foreign body associated.
- When a “**biofilm active**” agent was added as a 2nd antibiotic.
 - Rate of death or SAB-related late complications within **180 days** (HR 0.53, 95% CI 0.35-0.79) and a lower **90 day** mortality (HR 0.57, 95% CI 0.36-0.91)
- **Avoid “Moxi-Doxy?”**
 - *Goldstein et.al. J. Med. Micro. 2008, 57, 452-456*

Enterococcal Bacteremia

- Data from a **retrospective cohort study** conducted in Australia revealed that glycopeptide administration instead of beta-lactams was an **independent risk factor for 30-day mortality**
 - *Foo et.al. JAC. 2014, 69, 2252-2257.*
- **Amp-resistant** enterococcus
 - The Wilcox study mentioned for SAB also included enterococcal CRBSI, and this found **linezolid non-inferior to vanc**
 - *Wilcox et.al. CID. 2009, 48-203-212*
- **VRE?**
 - A retrospective, propensity score-matched cohort study with 2630 patients who received **linezolid** or **daptomycin** for VRE bacteremia or endocarditis revealed that daptomycin group had lower mortality only for endocarditis; patients in daptomycin arm experienced fewer adverse effects, too
 - Dapto was dosed at 6 mg/kg
 - *Britt et.al. Antimicrob. Agents Chemother. 2017, 61, e02216-16*
- Is Linezolid truly one size fits all?
 - Should consideration be given to renal dosing, hepatic dosing, and TDM in critically ill patients?

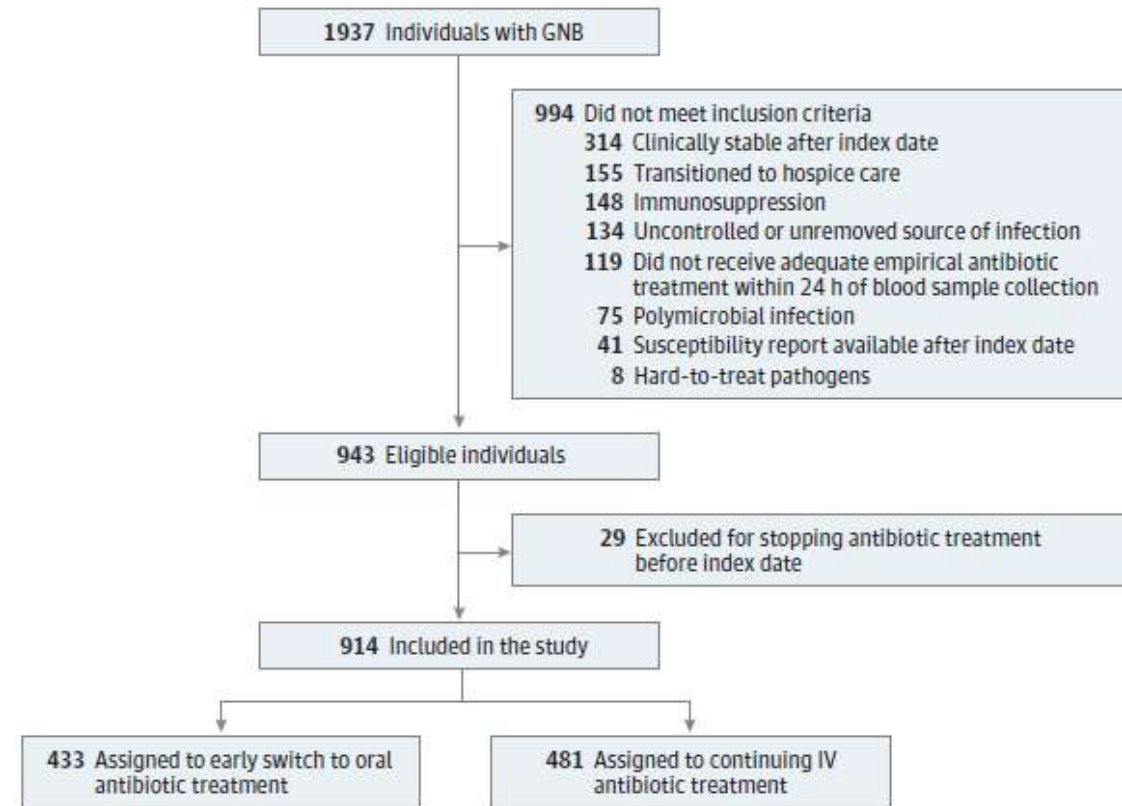
Food for Thought? Amoxicillin PK/PD Data

- There is a **saturable**, probably **capacity-limited** and **carrier-mediated** mechanism of transport from the intestine to the circulation.
- **Amoxicillin bioavailability is dose-dependent:**
 - From almost 100% for a 375 mg dose to 55% for a 3000 mg dose.
 - A pk/pd study for **pyelonephritis** model found:
 - Modest target of 32.5% fT > MIC, PTA is <90% for a 1000 mg tid regimen when MIC is > 2 mg/L
 - Catrall et.al. *Eur. J. Clin. Microbiol. Infec. Dis.* 2019, 38, 2311-2321
 - A recent publication claims that maybe lower doses (750 mg tid) are sufficient for 50%fT > MIC if MIC ≤ 2 mg/L
 - Van Den Broek et.al. *JAC* 2023, 78, 389-396

What About Gram-Negative Bacteremia?

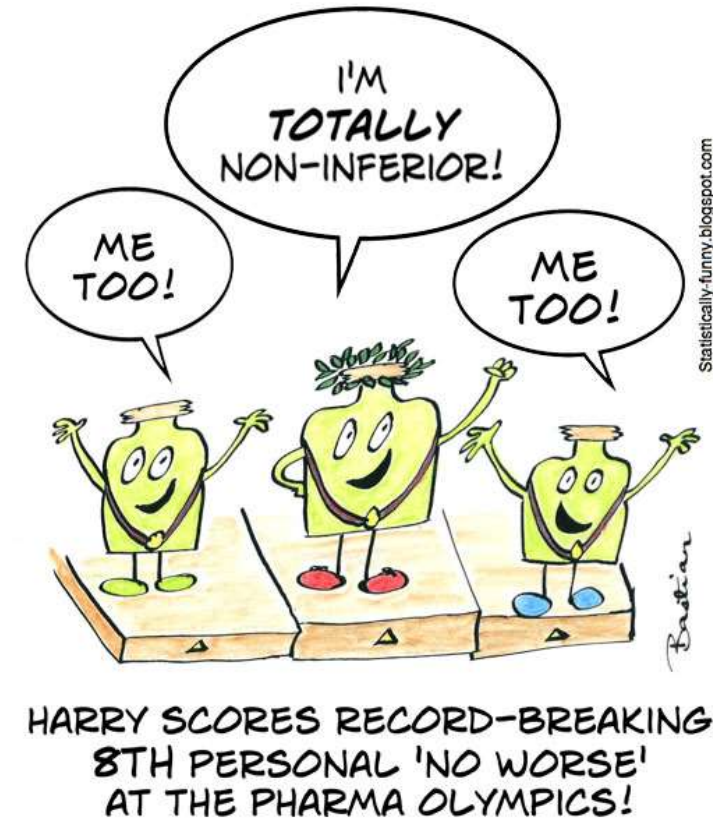
- ***Tingsgard et.al. JAMA Network Open. 2024;7(1):***
 - Adults with **uncomplicated GNRB** in Copenhagen Denmark
 - Short course IV with switch to oral vs “longer” course IV
 - Looked at 90 day all-cause mortality
 - The proportion of individuals who died was higher in the group receiving prolonged IV treatment (**69 [14.3%] vs 30 [6.9%]**)
 - Referenced the **INVEST trial** and **SOAB trial** (both for uncomplicated GNRB)
- **Target trial emulation** offers a promising complement to RCTs by leveraging existing data sources to emulate the design and analysis of a hypothetical target trial
- **The inclusion of immunosuppressed individuals** (n = 77) expanded the sample size to 991.
 - Thirty-five individuals with immunosuppression (**45.5%**) received early **oral stepdown** treatment, while 42 (54.5%) received prolonged IV treatment.
 - The results of the intention-to-treat and per-protocol analyses were consistent with those of the main analysis.

Figure 1. Selection of Individuals With Gram-Negative Bacteremia (GNB) for the Target Trial Emulation



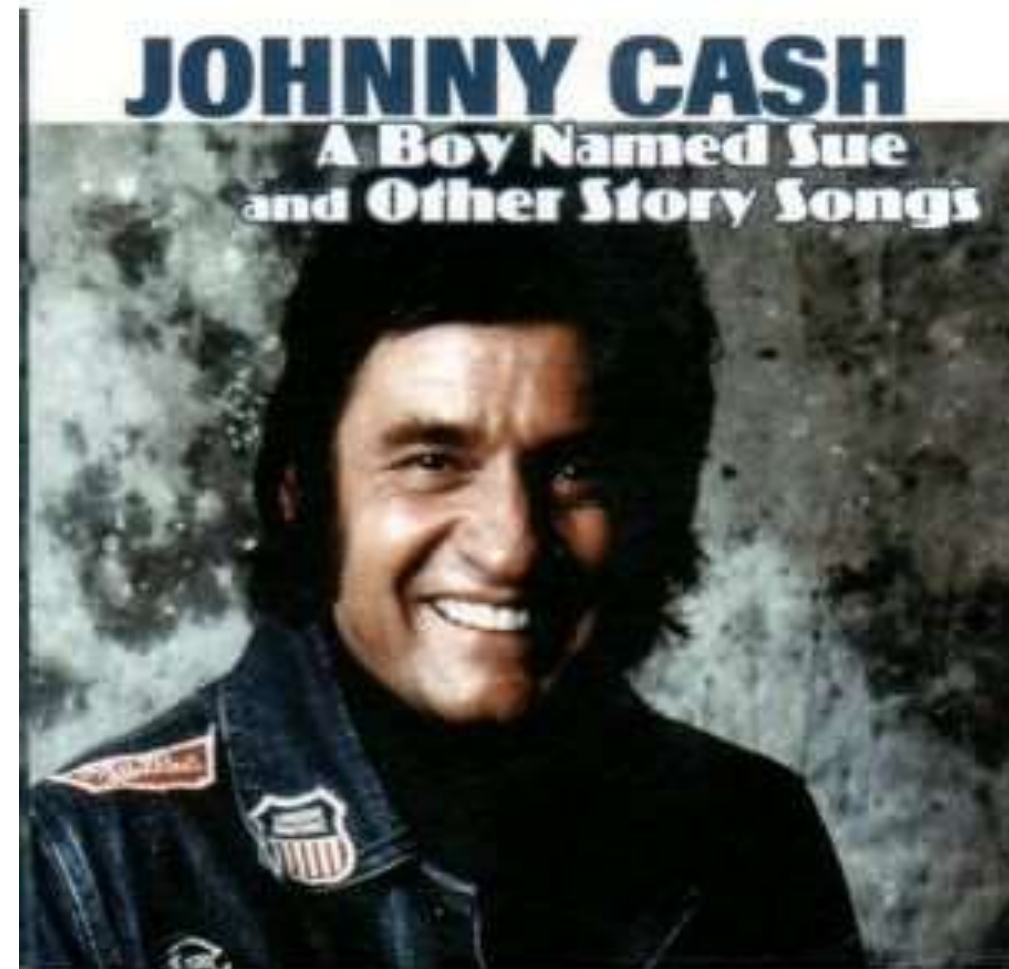
What About ESBL's and Amp C Producers?

- In a **meta-analysis**, oral or IV fluoroquinolones were **non-inferior** to other antibiotics when used as definitive therapy for ESBL-producing strains, if quinolone susceptible;
 - Vardakas et.al. *J.Antimicrob. Chemother.* **2012**, 67, 2793–2803
- Similar outcomes for fluoroquinolones or **TMP/SMX** versus carbapenems were observed against ESBL or AmpC producers
 - Meije et. al. *Int. J.Antimicrob. Agents* **2019**, 54, 189–196.



What About “A Boy Named Pseu?”

- A retrospective study with **Pseudomonas bacteremia** cases revealed that 28-day mortality rate stratified by APACHE II and Pitt bacteremia score was **not statistically different** between patients who were treated with fluoroquinolone or antipseudomonal beta-lactam
 - Received a median of **6d of IV** before oral switch
 - *Wu et.al. Infection 2018, 46, 365-373*
- In addition, retrospective data for Pseudomonas bacteremia derived from a **systematic review and meta-analysis** did not show any worse outcomes in subjects who received fluoroquinolones.
 - *Reid et.al. Antibiotics 2021, 10, 1483*

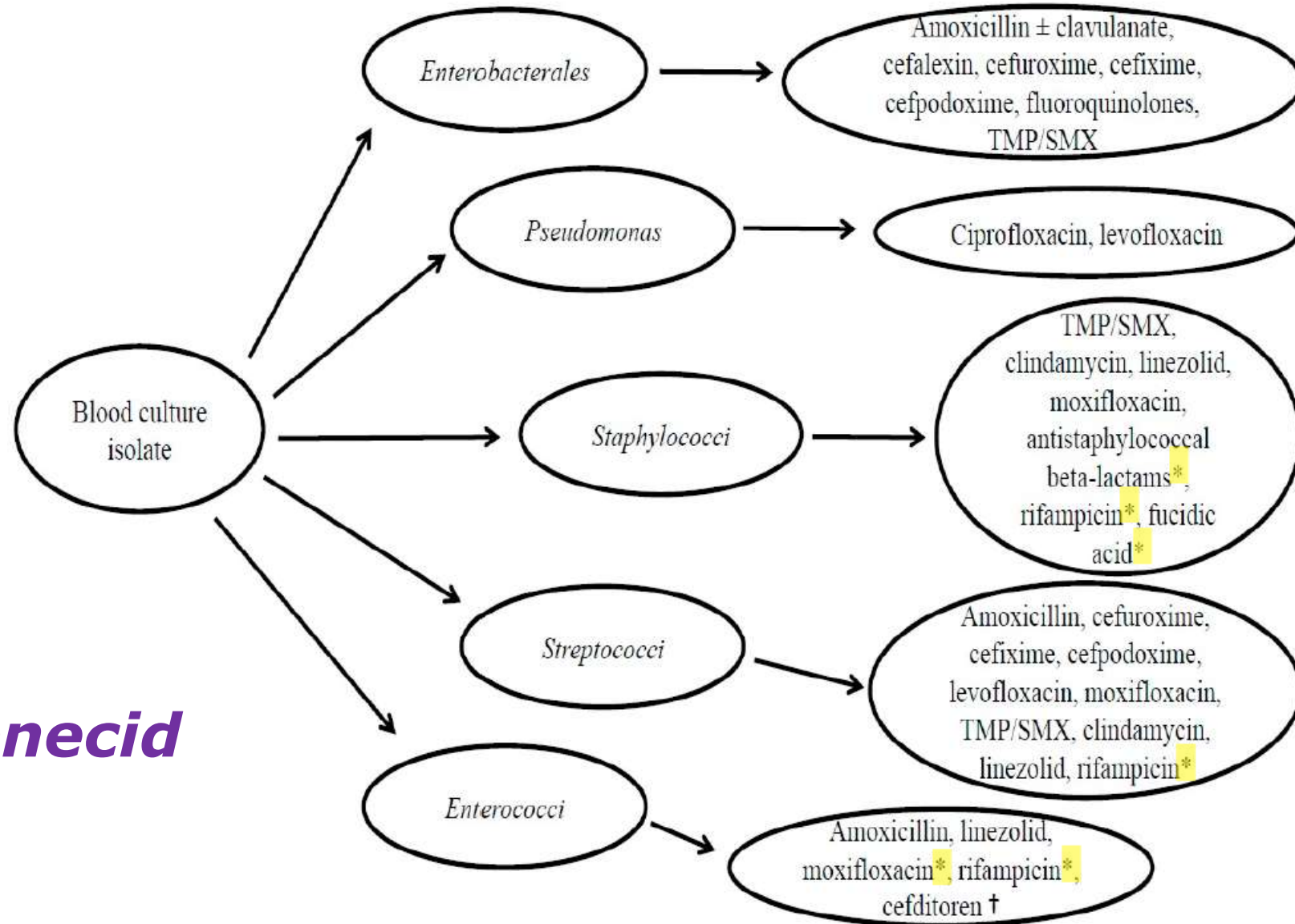


So, Where Does That Leave Us?

MY HEAD'S ALL
TIED UP LIKE...
A PRETZEL!
I GOT PRETZELS
IN MY HEAD!



Probenecid



Fosfomycin

Figure 1. Oral antibiotic options for bacteremia and endocarditis according to causative pathogen, provided that PK/PD targets can be achieved given the MIC. * Only combined with another active antibiotic. † Only as an adjunct treatment against *E. faecalis*. List of abbreviations: TMP/SMX,

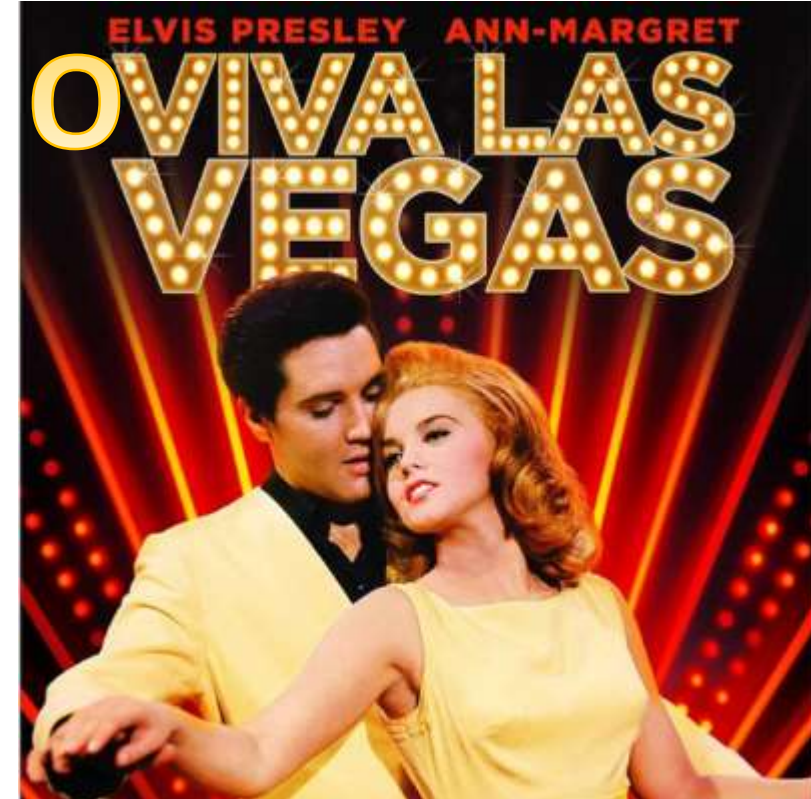
BUT WAIT



THERE'S MORE

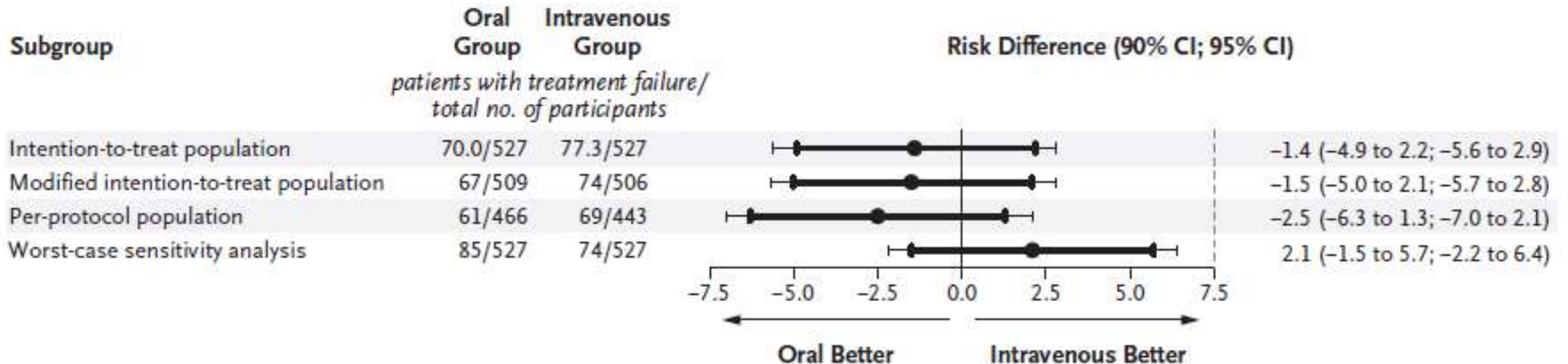
OVIVA

- Multicenter open label, parallel group, randomized controlled non-inferiority trial
- Adults (> 17 yo)
- **Diagnoses included:** native OM of the extraaxial skeleton, native joint infection requiring excision arthroplasty, PJI, orthopedic fixation device infection, or vertebral osteomyelitis with or without associated diskitis or soft-tissue infection.
- **Primary Endpoint:** definite treatment failure w/in 1 yr after randomization
- **Secondary Endpoints:** Probable or possible treatment failure, early dc of randomly assigned therapy, catheter complications, C. diff, serious adverse events,



OVIVA Continued

- *Glycopeptides* (41.4%) and *Cephalosporins* (37.6%) in the IV
- *Quinolones* (43.8%) and combination oral (14.1%) in the oral
- *Rifampin* use (15.5% with IV vs 51.5% with po)
- Total treatment duration **did not differ** between the groups





Partial Oral Therapy for Osteomyelitis and Endocarditis — Is It Time?

Helen W. Boucher, M.D.

- She looked at both OVIVA and POET.
- **Strengths:** use of real-world inclusion criteria, allowance for standard surgical and medical therapies, diagnostic rigor, involvement of expert physicians, close clinical monitoring (two to three outpatient visits per week in the POET trial), and relatively long — and little loss to — follow-up.
- **Weaknesses:** open-label design (mitigated by use of adjudication committees who were not aware of the treatment assignments), multiple pathogens and treatment regimens (single agent and combination therapies), heterogeneous populations (bone and joint infections with or without hardware, variable surgical interventions in the OVIVA trial, and native and prosthetic valve infective endocarditis on the left side of the heart with or without surgery in the POET trial), and inclusion of few antibiotic-resistant organisms,
- **Final Opinion:** It is **premature** to recommend a widespread early switch to oral therapy for bone and joint infection or step down to combination oral antibiotic therapy for infective endocarditis on the left side of the heart

Question 2. How often do you transition from intravenous to oral antibiotic therapy for patients with IE?

Never	71 (16%)
Rarely ($\leq 10\%$ of cases)	242 (53%)
Occasionally (11-25% of cases)	97 (21%)
Frequently (26-50% of cases)	26 (6%)
Very frequently ($> 50\%$ of cases)	16 (4%)

Question 3. Please select the THREE factors below that most influence your decision whether to transition to oral therapy for IE:

[Note: 32/424 respondents selected > 3 factors]

[Select all that apply; numbers add to $> 100\%$]

[answered by 424]

Availability of oral antibiotic options with appropriate spectrum	316 (75%)
Pathogen	291 (69%)
Clearance of bloodstream infection	190 (45%)
Adherence potential to oral therapy with follow-up	183 (43%)
Desire to avoid prolonged intravascular use	168 (40%)
Prosthetic valve or prosthetic valve material	92 (22%)
Imaging evidence of stable or improving valvular infection	13 (3%)

Open-text field for comments/other factors (66 responses):

http://www.int-med.uiowa.edu/Research/EIN/Q3_factors.pdf

Question 4. For which pathogens do you feel comfortable transitioning to oral therapy?

[Select all that apply; numbers add to $> 100\%$]

[answered by 444]

N/A, do not transition to oral therapy	85 (19%)
<i>Streptococcus</i> spp.	292 (66%)
Gram-negative bacilli	231 (52%)
HACEK (<i>Haemophilus</i> , <i>Aggregatibacter</i> , <i>Cardiobacterium</i> , <i>Eikenella</i> , <i>Kingella</i>)	133 (30%)
MSSA	124 (28%)
Coagulase-negative staphylococci	121 (27%)
<i>Enterococcus</i> spp.	92 (21%)
MRSA	84 (19%)

Question 5. The POET trial used transitional oral antibiotic therapy with two antibiotics (combination therapy). In your practice, which best describes your usual approach?

I do not use transitional oral antibiotic therapy	142 (31%)
I always use two oral antibiotics until completion of therapy	76 (17%)
I typically use a single oral antibiotic unless the pathogen specifically requires two antibiotics (e.g. <i>C. burnetii</i> , <i>Bartonella</i> IE)	230 (51%)
[not answered]	4 (0.9%)

Question 6. What are the primary issues that prevent you from prescribing transitional oral therapy for IE?

[Select all that apply; numbers add to >100%]

[answered by 447]

Fear of treatment failure or recurrence	322 (72%)
Concerns about patient adherence	235 (53%)
Lack of sufficient evidence	214 (48%)
Patient comorbidities (e.g. gastrointestinal absorption issues)	175 (39%)
Medicolegal issues	145 (32%)
Institutional guidelines or restrictions	40 (9%)
None, I use transitional oral therapy regularly	26 (6%)

Open-text field for comments/other concerns (56 responses):

http://www.int-med.uiowa.edu/Research/EIN/Q6_barriers.pdf

Question 7. Which choice best describes your approach to transitioning from IV to oral therapy in people who inject drugs (PWID) with IE?

I never consider an oral switch	35 (8%)
I rarely consider an oral switch	82 (18%)
I occasionally consider an oral switch	172 (38%)
I often consider an oral switch	118 (26%)
I always consider an oral switch	38 (8%)
[not answered]	7 (2%)

Question 8. How strongly do current guidelines (e.g. AHA, ESC) influence your decision to consider transitional oral therapy for infective endocarditis?

Not at all	29 (7%)
Slightly	82 (18%)
Moderately	178 (39%)
Strongly	118 (26%)
Very strongly	42 (9%)
[not answered]	3 (0.7%)

Question 9. What would increase the likelihood of incorporating transitional oral therapy into your practice?

[Select all that apply; numbers add to >100%]

[answered by 447]

N/A, will not use transitional oral therapy	4 (0.9%)
Clearer guidelines or consensus statements	336 (75%)
More prospective clinical trial data	316 (71%)
Improved methods to monitor patient adherence	155 (35%)
Access to oral antibiotic regimens with appropriate coverage	144 (32%)
Institutional protocols or support	108 (24%)

PRISMA

HEALTHSM



Questions?

Thank you



So, What Preceded POET?



Oral Antibiotics For IE: A clinical Review

Brown et.al. JAC 2020; 75: 2021–2027

- Given things like a high bacterial density and risk of inoculum effect, a goal of reaching an **MIC/MBC ratio of 1:8** is recommended in general.
- Factors such as **concentration dependent vs time-dependent killing** and **post-antibiotic effect** must also be considered.
- The peak levels achieved by **amoxicillin** and **flucloxacillin** after either oral or IV administration comfortably exceed the published MIC values for the majority of common IE organisms
- The AUC of **oral** amoxicillin as a percentage of the same IV dose was 93% for a 500mg dose and 89% for a 1 g dose.

Table 1. Pharmacokinetic and pharmacodynamic properties of amoxicillin given orally (PO) and IV^{11–13}

Property	Amoxicillin	
	IV	oral
Peak serum levels	83–112 mg/L, 1 min after 500 mg IV injection	8–10 mg/L, 2 h after 500 mg PO dose
Duration of effective plasma concentration	after 500 mg IV dose, plasma concentration fell to 1 mg/L after 3.5 h	after 500 mg PO dose, concentration fell to zero after 6–8 h
Excretion	mainly urinary (58%–68% of PO dose excreted unchanged in urine during first 6 h)	
Pharmacokinetics	bioavailability 76.5%; low protein binding (17%)	
Published MIC values		
<i>S. aureus</i> (penicillin susceptible)	0.1 mg/L	
α-haemolytic streptococci	0.01 mg/L	
<i>E. faecalis</i>	0.5 mg/L	

Table 2. Pharmacokinetic and pharmacodynamic properties of flucloxacillin given orally and IV^{14–17}

Property	Flucloxacillin	
	IV	oral
Peak serum levels	86.8 mg/L after 500 mg IV dose (immediately after injection)	14.5 mg/L, 1 h after 500 mg PO dose
Duration of effective plasma concentration	6 h after 500 mg IV dose plasma levels fell below 1.0 mg/L	4 h after 500 mg PO dose, plasma level 2.2 mg/L; 6 h after 500 mg PO dose, plasma level <1.0 mg/L in non-fasting subjects
Excretion	mainly urinary excretion (50% of dose recovered in urine over 0–6 h)	
Pharmacokinetics	bioavailability 54% (±18%); 92%–95% protein bound	
Published MIC values		
<i>S. aureus</i> (penicillin susceptible)	0.1–0.25 mg/L	
β-haemolytic streptococci	0.05–0.1 mg/L	
<i>E. faecalis</i>	25 mg/L	
Published MBC values		
<i>S. aureus</i> (penicillin susceptible)	0.2 mg/L	
<i>Streptococcus pyogenes</i>	0.4 mg/L	

Heldman et al. Am J Med 1996; 101: 68–76. (1996)

- Randomized non-blinded trial looking at **febrile IVDUs** with suspicion of IE:
 - Randomized to either oral (cipro and rifampin) or IV (oxacillin or vanc plus 5 days of gent) while awaiting BC's
- Out of 573 pts, 85 had staph bacteremia (**79 had SA**).
 - Of these 85, **44 had suspected right-sided IE**
 - 19 were treated oral and 25 treated with IV at least 28 days.
 - Only 6% had oxacillin resistant staph.
 - There were four **treatment failures** total (3 oral and 1 IV) but no statistically significant difference in outcomes ($p = 0.6$).
 - Treatment toxicity (hepatotoxicity or nephrotoxicity) in the IV vs oral group: **61.5% versus 2.8%** ($P < 0.0001$).

- Randomized 30 pts with **PCN susceptible streptococcal endocarditis** to:
 - Ceftriaxone for 4 weeks vs
 - Ceftriaxone for 2 wks and amoxicillin for 2 wks.
 - **Excluded “complicated cases”** (CHF, severe AR, rec thromboembolic, or PVIE)
 - All had left-sided IE
 - Strep MIC **< 0.12 mg/L** for PCN and **< 0.25 mg/L** for Ceftriaxone
- All patients were “cured” and 380 hospital days saved

Additional Observational Studies

- **Tissot-Dupont et al. (2019):**

- Staph Aureus IE at one center over 16 yrs with ~ 170 in each arm.
 - *Vanc* or *oxacillin* (w/ gent x 1) vs
 - 1 wk of IV **co-trimoxazole** and **clindamycin** followed by 5 wks of oral co-trimoxazole. (39 in oral received **rifampin** and **gent** as well)
 - Control group having a higher incidence of vegetations (82% vs 64%) and a higher incidence of fever (89% vs 78%).
 - The oral antibiotic group also had a 2-fold lower in-hospital mortality rate and 30 day mortality rate, although the 90 day mortality rate was similar in the two groups.
 - Oral group had 10 microbiological failures

- **Parker and Fossieck et.al. (1980):**

- Staph Aureus IE in 33 pts (**29 with IVDU**) with oral therapy after a mean of 16 days IV (and “clinically well”)
- Peak and trough measurements ensuring MICs and MBCs were met
- All patients in the case series were cured and had negative BC’s at 6 mo f/u

Table 1. Oral antibiotic dosages for bacteremia and infective endocarditis/beta-lactams.

Oral Antibiotic	Microorganism	MIC (mg/L)	Dosage	Dose Adjustment for Special Populations	References
Amoxicillin	<i>Enterobacterales</i> ; <i>Streptococci</i> ; <i>Enterococci</i>	≤ 1 1–2 > 2	1 g tid 1 g qid Avoid	eGFR ≤ 10 mL/min or dialysis-dependent patients: 1 g bid	[40,44–47]
AMX/CLAV	<i>Enterobacterales</i>	≤ 2 > 2	1000/125 mg tid Avoid	eGFR ≤ 10 mL/min or dialysis-dependent patients: 1000/125 or 875/125 mg bid	[42,46,48]
Cefalexin	<i>Enterobacterales</i>	≤ 1.5 ≤ 3 > 3	1 g tid 1 g qid Avoid	eGFR 10–30 mL/min: 1 g tid eGFR ≤ 10 mL/min or dialysis-dependent patients: 1 g bid	[43,49]
Cefuroxime axetil	<i>Enterobacterales</i> ; <i>Streptococci</i>	≤ 0.5 > 0.5	500 mg tid Avoid	None	[41]
Cefixime - Cefpodoxime	<i>Enterobacterales</i> ; <i>Streptococci</i>	≤ 0.5 > 0.5	400 mg bid Avoid	None	[40,41]

Table 2. Oral antibiotic dosages for bacteremia and infective endocarditis/non-beta-lactams.

Oral Antibiotic	Microorganism	MIC (mg/L)	Dosage	Dose Adjustment for Special Populations	References
Ciprofloxacin	<i>Enterobacterales</i> ; <i>Pseudomonas</i>	≤0.125 0.25 >0.25	500 mg bid 750 mg bid Avoid	eGFR ≤ 30 mL/min: 25% dose reduction Obesity: no dose modification	[10,56,58,121]
Levofloxacin	<i>Enterobacterales</i> ; <i>Pseudomonas</i> ; <i>Streptococci</i>	≤1 >1	Dose guided by creatinine clearance based on ideal body weight Avoid	≤30 mL/min: 500 mg qd 30–90 mL/min: 750 mg qd >90 mL/min: 500 mg bid	[122–124]
Moxifloxacin	<i>Enterobacterales</i> ; <i>Streptococci</i> <i>Staphylococci</i>	≤0.25 >0.25 ≤0.06 0.125 >0.125	400 mg qd Avoid 400 mg qd Use in combination with another agent or 800 mg/day, preferably with TDM Avoid	Renal impairment or obesity: no dose modification	[83,84,125]
TMP/SMX	<i>Enterobacterales</i> ; <i>Streptococci</i> ; <i>Staphylococci</i>	≤1 (as TMP concentration [=20 mg/L TMP/SXT]) >1	10 mg/kg/day (TMP component) divided in 2–3 doses Avoid	eGFR ≤ 30 mL/min: 50% dose reduction	[126,127]
Clindamycin	<i>Staphylococci</i> ; <i>Streptococci</i>	≤0.25 >0.25	600 mg tid Avoid	Bone source of bacteremia and either body weight >75 kg or MIC = 0.25 mg/L: 900 mg tid	[70,76,77,79,128,129]

Oral Antibiotic	Microorganism	MIC (mg/L)	Dosage	Dose Adjustment for Special Populations	References
Linezolid	<i>Staphylococci</i> ; <i>Streptococci</i> ; <i>Enterococci</i>	<2 2 >2	600 mg bid Use in combination if possible or use TDM Avoid	eGFR $\leq$ 60 mL/min, Child-Pugh C cirrhosis or INR > 2 due to hepatic impairment: 300 mg bid Dialysis-dependent patients: 300 mg bid or 600 mg qd eGFR $\geq$ 120 mL/min: avoid Obesity plus eGFR $\leq$ 60 mL/min: 600 mg bid Obesity plus eGFR $\geq$ 60 mL/min: 450 mg tid If body weight is >140 kg, use only if MIC $\leq$ 1 mg/L	[112,113,116-120,130–135]
Rifampicin	<i>Staphylococci</i> ; <i>Streptococci</i> ; <i>Enterococci</i> (adjunct treatment)	≤ 0.06	300 mg tid	None	[136,137]
Metronidazole	Anaerobes	≤ 4	Infections outside central nervous system: 500 mg bid	Obesity: 500 mg tid	[138–140]

2077 Participants were assessed for eligibility

628 Were not eligible
125 Had concomitant infection requiring intravenous therapy
182 Had mild disease that could be treated with <6 wk of antibiotics
80 Had no suitable oral regimen available
10 Had previous enrollment in the trial
28 Had shock or other features requiring long-term intravenous therapy
74 Were unlikely to adhere to trial requirements
6 Had mycobacterial, fungal, parasitic, or viral infection
122 Had reasons not reported

1449 Were eligible

395 Did not undergo randomization
72 Preferred intravenous treatment
44 Preferred oral treatment
6 Had surgeons who did not want them to participate
10 Left to go abroad
27 Transferred to another hospital
49 Had other reason
187 Declined to participate without providing further reason

1054 Underwent randomization

527 Were assigned to the intravenous group
458 Received at least 4 wk of their assigned treatment strategy

22 Did not complete follow-up
7 Withdrew from trial
5 Were lost to follow-up
10 Died

527 Were included in the primary intention-to-treat analysis
506 Were included in the modified intention-to-treat population
21 Did not have end-point data

84 Were excluded from per-protocol analysis
15 Were missing end-point data
63 Had <4 wk of assigned strategy for reasons other than possible or probable recurrence
6 Had both missing data and <4 wk of assigned strategy

443 Were included in the per-protocol analysis

527 Were assigned to the oral group
478 Received at least 4 wk of their assigned treatment strategy

20 Did not complete follow-up
7 Withdrew from trial
7 Were lost to follow-up
6 Died

527 Were included in the primary intention-to-treat analysis
509 Were included in the modified intention-to-treat population
18 Did not have end-point data

61 Were excluded from per-protocol analysis
13 Were missing end-point data
43 Had <4 wk of assigned strategy for reasons other than possible or probable recurrence
5 Had both missing data and <4 wk of assigned strategy

466 Were included in the per-protocol analysis

been successfully treated with oral penicillin. Iversen et al. and Li et al. finally conducted randomized, controlled trials to document that oral antibiotics effectively treat endocarditis and osteomyelitis. Given the appropriate historical context, such therapy is no longer premature but rather decades overdue.

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prosthetic-valve endocarditis were included, of whom only 7 received partial oral therapy. In view of this, we think the conclusion should be more refined. We strongly urge against implementation of partial oral antibiotic treatment for nonstreptococcal or prosthetic-valve endocarditis.

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excluded, which raises questions about the generalizability of the results. The antimicrobial susceptibility among the infecting organisms in the trial was an American doctor's dream! Endocarditis caused by *S. aureus* or *S. epidermidis* is often associated with methicillin resistance, but not in this trial. This oral treatment approach should be attempted with caution in the United States.

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We agree with Verkaik et al. that our trial was powered to assess the primary outcome for the whole trial population. In the prespecified subgroup analyses, we found a reassuring homogeneous pattern of outcomes with no interaction for any of the subgroups. Our follow-up of these patients continues to show noninferiority of partial oral therapy.¹ These data, the results from the OVIVA trial by Li et al. of bone and joint infections treated with oral antibiotics, and the lack of other findings supporting superiority of full-length intravenous antibiotics do not support Verkaik and colleagues' cautiousness — provided that appropriate levels of orally administered antibiotic in blood are achieved.

Lauter and Saravolatz question the generalizability of the POET trial, since only 20.5% of the screening population was included. It is noteworthy that 21.9% of those screened did not meet diagnostic criteria for endocarditis, 15.5% were unwilling to participate, 8.9% had endocarditis due to other bacteria, and 3.6% died before randomization — that is, a total of 50% did not make it past screening for clinical reasons rather than for reasons related to the design of the trial. Patients undergoing surgery were included irrespective of the presence of bacteria on operative specimens. In geographic areas with higher incidences of antibiotic resistance, the proposed trial criteria are still applicable, but fewer effective antibiotics will be available. If two oral antibiotics with antimicrobial susceptibility are identified, we believe that this oral treatment approach still applies.