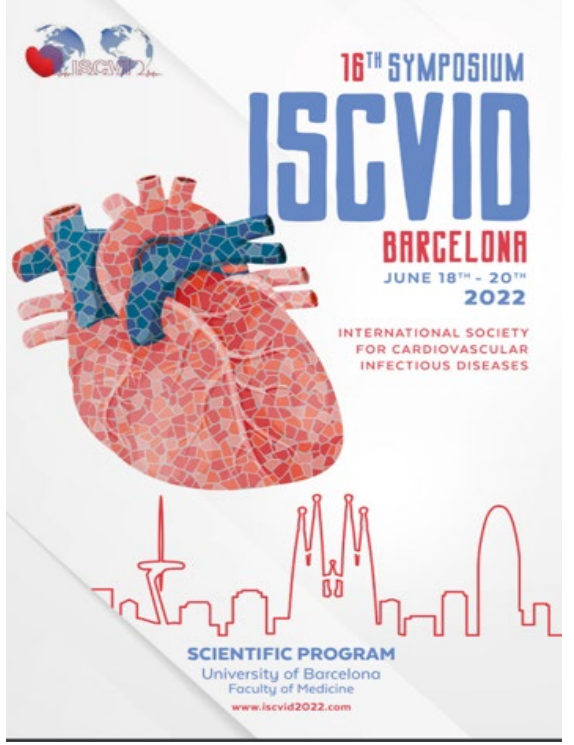
POETIC LICENCE

16th ISCVID meeting June 2022
Barcelona



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Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

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ABSTRACT

POET - strengths

- Well designed
- Multi-centre
- Balanced groups 200 each arm
- Range of pathogens: Strep, Staph, Enterococci
- Very early surgery 38% median 2 days from diagnosis
- Mortality rate very low - 5% overall
- Comprehensive follow up to 6 months
- Composite outcomes of great interest

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 — $\times 10^{-9}$/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 study - limitations

- Not multi-national
- Patient selection - highly restricted, very large number exclusions
- Not generalisable
- Complex IE excluded
- AMR excluded
- Predominantly enteric Streptococci 50%
- Few cases of PVIE 107 (27%) *S aureus* 11 cases (10% of PVIE)
- PVIE that had surgery - 22%/19%

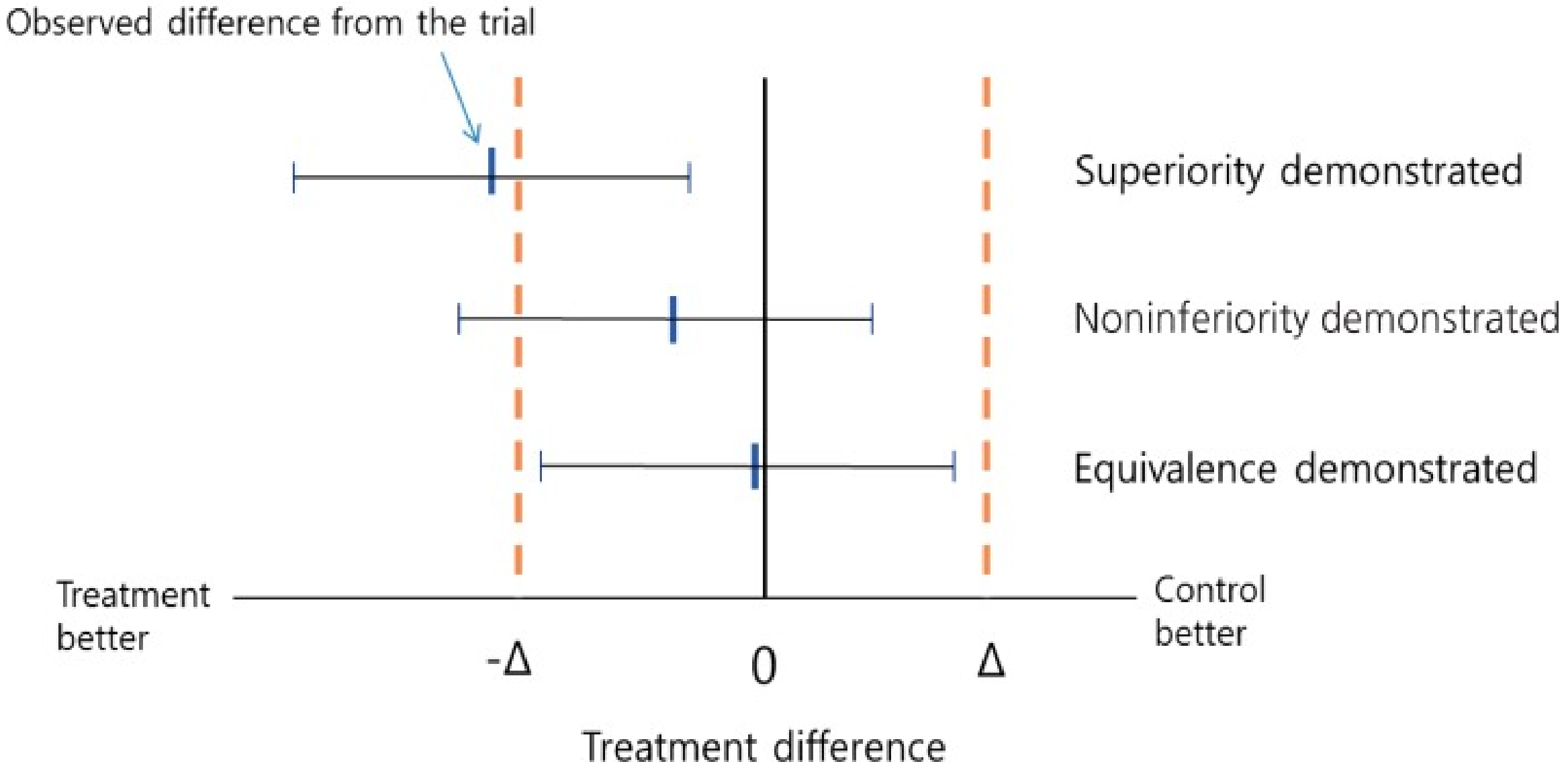
POET study - limitations

- Planned - early stabilization LSIE randomisation after completed at least 10 days IV therapy and at least 7 days post surgery
- High rates of very early surgery - 38%
- Median time diagnosis to surgery 2 days (IQR 1-9) in IV treated patients and 2 days (IQR 1-6) in the oral treated patients.
- Resulting - time from surgery to randomization 16 days (IQR 13-18) in IV treated patients and 17 days (IQR13-22) in oral treated patients.

POET study - limitations

- Composite outcome measures versus only mortality or relapses
- Null hypothesis is that oral treatment will be less effective than IV by 10% equivalence margin of composite outcomes
- Sample size is too small for individual outcomes – potential type 2 error

95% Confidence interval noninferiority



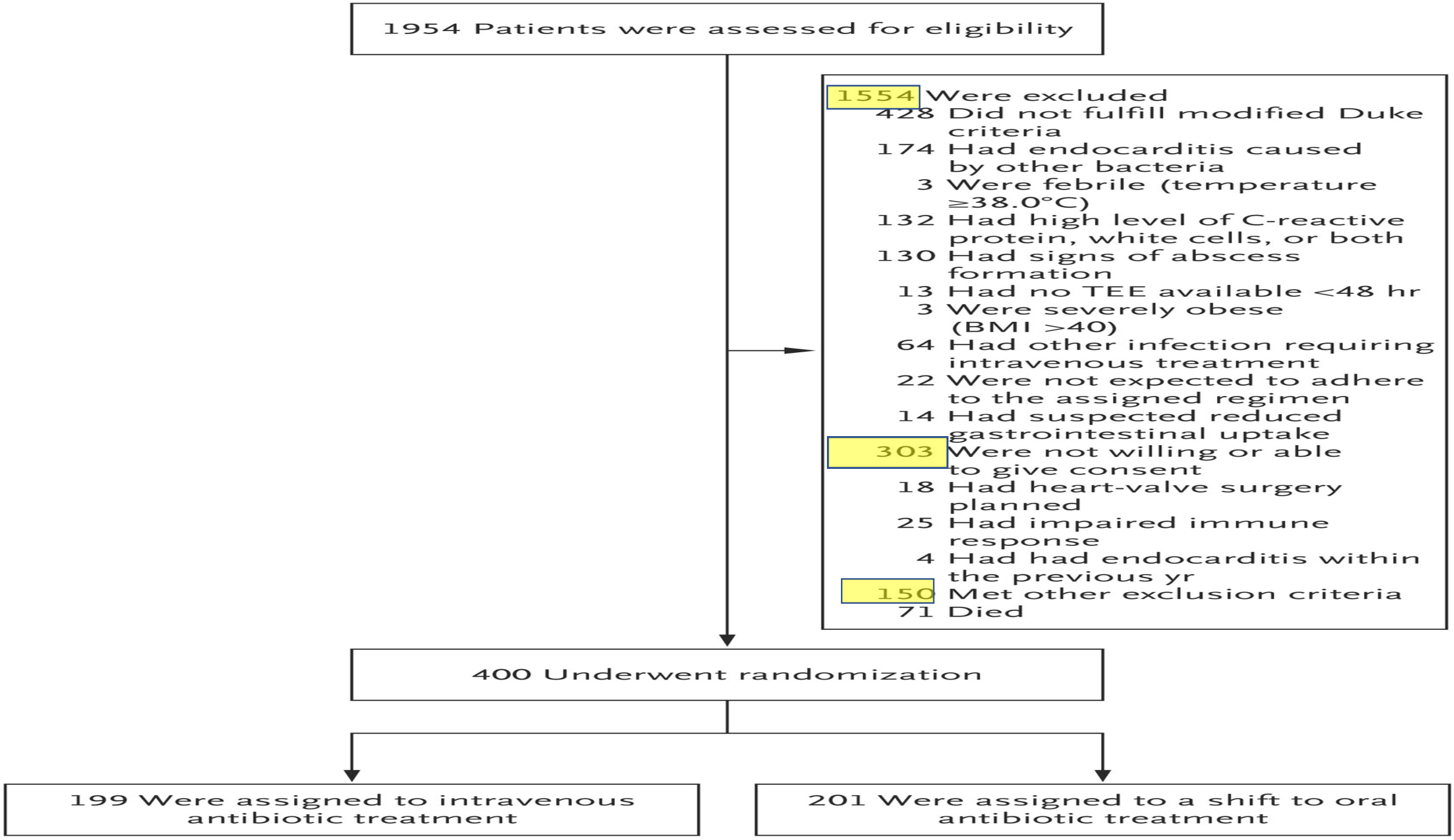

1954 Patients were assessed for eligibility
1554 Were excluded
428 Did not fulfill modified Duke criteria
174 Had endocarditis caused by other bacteria
3 Were febrile (temperature ≥38.0°C)
132 Had high level of C-reactive protein, white cells, or both
130 Had signs of abscess formation
13 Had no TEE available <48 hr
3 Were severely obese (BMI >40)
64 Had other infection requiring intravenous treatment
22 Were not expected to adhere to the assigned regimen
14 Had suspected reduced gastrointestinal uptake
303 Were not willing or able to give consent
18 Had heart-valve surgery planned
25 Had impaired immune response
4 Had had endocarditis within the previous yr
150 Met other exclusion criteria
71 Died
400 Underwent randomization
199 Were assigned to intravenous antibiotic treatment
201 Were assigned to a shift to oral antibiotic treatment

Table S11

Susceptibility to penicillin, ampicillin or methicillin for the bacterial groups included

	Penicillin susceptibility streptococci (MIC < 1 mg/L)	Penicillin susceptibility staphylococci (large and tapered penicillin zone. Penicillinase induction test)	Ampicillin susceptibility (MIC ≤ 4 mg/L)	Methicillin resistance (Cefoxitin or oxacillin screening. Confirmed by mec gene analysis)
*Streptococcus spp**	194 susceptible 2 resistant			
Enterococcus faecalis			96 susceptible 1 resistant	
Staphylococcus aureus		27 susceptible 60 resistant		87 susceptible 0 resistant
Coagulase negative staphylococci		7 susceptible 16 resistant		15 susceptible 8 resistant

*Including 1 isolates of *Abiotrophica defectiva*.

The present table presents the four major bacterial groups included in the study with respect to

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)

* Six patients, three in each group, had two outcomes.

† For details about relapse of the positive blood culture, see the Supplementary Appendix.

Duration of therapy before randomisation

- Median time from the diagnosis of IE to randomization was 17 days IV group (IQR 13 to 23)
- 17 days in the oral group (IQR 12 to 24)
- 2-3 weeks
- After randomization, patients were treated according to the assigned regimen for a median of 19 days IV group (IQR 14 to 25)
- 17 days in the oral group (IQR 14 to 25)
- Total 5 weeks

Table 16 Antibiotic treatment of infective endocarditis due to oral streptococci and *Streptococcus bovis* group[a]

Antibiotic	Dosage and route	Duration (weeks)	Class[b]	Level[c]	Ref.[d]	Comments
Strains penicillin-susceptible (MIC ≤ 0.125 mg/L) oral and digestive streptococci						
Standard treatment: 4-week duration						
Penicillin G or	12–18 million IU/day i.v. either in 4–6 doses or continuously	4	I	B	6,8, 135–139	Preferred in patients > 65 years or with impaired renal or VIII (vestibulocochlear) cranial nerve functions. 6-week therapy recommended for patients with PVE
Amoxicillin[e] or	100–200 mg/kg/day i.v. in 4–6 doses	4	I	B		
Ceftriaxone[f]	2 g/day i.v. or i.m. in 1 dose	4	I	B		
	Paediatric doses:[g] Penicillin G 200,000 IU/kg/day i.v. in 4–6 divided doses Amoxicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Ceftriaxone 100 mg/kg/day i.v. or i.m. in 1 dose					
Standard treatment: 2-week duration						
Penicillin G or	12–18 million IU/day i.v. either in 4–6 doses or continuously	2	I	B	6,8, 127, 135–138	Only recommended in patients with non-complicated NVE with normal renal function.
Amoxicillin[e] or	100–200 mg/kg/day i.v. in 4–6 doses	2	I	B		
Ceftriaxone[f] combined with	2 g/day i.v. or i.m. in 1 dose	2	I	B		
Gentamicin[h] or	3 mg/kg/day i.v. or i.m. in 1 dose	2	I	B		
Netilmicin	4–5 mg/kg/day i.v. in 1 dose	2	I	B		Netilmicin is not available in all European countries.
	Paediatric doses:[g] Penicillin G, amoxicillin, and ceftriaxone as above					

Table 17 Antibiotic treatment of infective endocarditis due to Staphylococcus spp.

Antibiotic	Dosage and route	Duration (weeks)	Class[a]	Level[b]	Ref.[c]	Comments
Native valves						
Methicillin-susceptible staphylococci						
(Flu)cloxacillin or oxacillin	12 g/day i.v. in 4–6 doses	4–6	I	B	68, 128, 135, 136, 158	Gentamicin addition is not recommended because clinical benefit has not been demonstrated and there is increased renal toxicity
	Paediatric doses:[d] 200–300 mg/kg/day i.v. in 4–6 equally divided doses					
Alternative therapy[e] Cotrimoxazole[f]	Sulfamethoxazole 4800 mg/day and Trimethoprim 960 mg/day (i.v. in 4–6 doses)	1 i.v. + 5 oral intake	IIb	C		[e]for Staphylococcus aureus
with						
Clindamycin	1800mg/day i.v. in 3 doses	1	IIb	C		
	Paediatric doses:[d] Sulfamethoxazole 60 mg/kg/day and Trimethoprim 12 mg/kg/day (i.v. in 2 doses) Clindamycin 40 mg/kg/day (i.v. in 3 doses)					
Penicillin-allergic patients[g] or methicillin-resistant staphylococci						
Vancomycin[h, ee]	30–60 mg/kg/day i.v. in 2–3 doses	4–6	I	B	68, 135, 136	**Cephalosporins** (cefazolin 6 g/day or cefotaxime 6 g/day i.v. in 3 doses) are recommended for penicillin-allergic patients with non-anaphylactic reactions with methicillin-susceptible endocarditis
	Paediatric doses:[d] 40 mg/kg/day i.v. in 2–3 equally divided doses					
Alternative therapy[ee]: Daptomycin[i,ff]	10 mg/kg/day i.v. once daily	4–6	IIa	C		**Daptomycin** is superior to vancomycin for MSSA and MRSA bacteraemia with vancomycin MIC > 1 mg/L
	Paediatric doses:[d] 10 mg/kg/day i.v. once daily					
Alternative therapy[e] [illegible]	[illegible]	1 i.v. + 5	IIb	C		

Table 18 Antibiotic treatment of infective endocarditis due to *Enterococcus* spp.

Antibiotic	Dosage and route	Duration, weeks	Class[g]	Level[h]	Ref.[i]	Comments
Beta-lactam and gentamicin-susceptible strains (for resistant isolates see [a,b,c])						
Amoxicillin[e] with Gentamicin[d]	200 mg/kg/day i.v. in 4–6 doses 3 mg/kg/day i.v. or i.m. in 1 dose	4–6 2–6[**]	I I	B B	68, 129, 135, 136, 186	6-week therapy recommended for patients with >3 months symptoms or PVE
	Paediatric doses[e] Ampicillin 300 mg/kg/day i.v. in 4–6 equally divided doses Gentamicin 3 mg/kg/day i.v. or i.m. in 3 equally divided doses					
Ampicillin with Ceftriaxone	200 mg/kg/day i.v. in 4–6 doses 4 g/day i.v. or i.m. in 2 doses	6 6	I I	B B	183–185	This combination is active against *Enterococcus faecalis* strains with and without HLAR, being the combination of choice in patients with HLAR *E. faecalis* endocarditis. This combination is not active against *E. faecium*
	Paediatric doses[e] Amoxicillin as above Ceftriaxone 100 mg/kg/12 h i.v. or i.m.					
Vancomycin[f] with Gentamicin[d]	30 mg/kg/day i.v. in 2 doses 3 mg/kg/day i.v. or i.m. in 1 dose	6 6	I I	C C		
	Paediatric doses[e] Vancomycin 40 mg/kg/day i.v. in 2–3 equally divided doses. Gentamicin as above					

HLAR: high-level aminoglycoside resistance; IE: infective endocarditis; MIC: minimum inhibitory concentration; PBP: penicillin binding protein; PVE: prosthetic valve endocarditis.
[d]High-level resistance to gentamicin (MIC >500 mg/L); if susceptible to streptomycin, replace gentamicin with streptomycin 15 mg/kg/day in two equally divided doses.

Table S7

Baseline demographics of patients undergoing heart valve surgery

	Intravenous treatment n=75	Oral treatment n=77
Age (years), mean (SD)	62.4 (8.7)	64.6 (8.2)
Gender (female), n (%)	14 (25.3)	14 (20.9)
Temperature (°C), mean (SD)	36.9 (0.47)	37.1 (0.40)
Co-morbidities		
Diabetes, n (%)	6 (8.0)	10 (13.0)
Renal failure, n (%)	5 (6.7)	2 (2.6)
Dialysis, n (%)	2 (2.7)	1 (1.3)
COPD, n (%)	3 (4.0)	3 (3.9)
Liver disease, n (%)	3 (4.0)	1 (1.2)
Cancer, n (%)	4 (5.4)	3 (3.9)
Drug user, n (%)	3 (4.0)	1 (1.3)
Microbiology		
Streptococcus spp, n (%)	39 (52.0)	38 (49.4)
***Enterococcus faecalis*, n (%)**	20 (26.7)	15 (19.5)
***Staphylococcus aureus*, n (%)**	10 (13.3)	16 (20.8)
Coagulase-negative staphylococci, n (%)	6 (8.0)	9 (11.7)
Biochemistry at randomization		
Haemoglobin (mM), mean (SD)	5.9 (0.89)	5.9 (0.78)
Leucocytes (10^9/L), mean (SD)	7.6 (2.1)	7.7 (2.2)
CRP (mg/L), mean (SD)	31.3 (18.6)	26.5 (15.6)
Creatinine, (µM), mean (SD)	106 (72)	102 (92)

Baseline demographics and characteristics of the patients undergoing heart valve surgery for endocarditis

Relapses

	IV	Oral
Worsening/relapse of infection, n (%)	2 (33.3)	2 (33.3)
Valve dysfunction, no infection, n (%)	3 (50.0)	4 (66.7)
Hematoma in the pericardium, n (%)	1 (16.7)	0 (0)
Type of embolic event	**3**	**3**
Cerebral emboli, n (%)	2 (66.7)	2 (66.7)
Emboli in the eye, n (%)	1 (33.3)	1 (33.3)
Details, patients with relapse of positive blood culture	**5**	**5**
Prosthetic valve, n (%)	2 (40.0)	3 (60.0)
Pacemaker, n (%)	0 (0)	1 (20.0)
Decreased susceptibility, n (%)	0 (0)	0 (0)
Streptococcus spp, n (%)	0 (0)	0 (0)
Enterococcus faecalis, n (%)	3 (60.0)	3 (60.0)
Staphylococcus aureus, n (%)	2 (40.0)	1 (20.0)
Coagulase-negative staphylococci, n (%)	0 (0)	1 (20.0)
Time from randomization to relapse (days), median (IQR)	25 (23-34)	94 (17-103)

Table S13

Breakdown of bacterial species for each of the elements of the composite outcome

	All-cause mortality		Unplanned cardiac surgery		Embolic event		Relapse of positive blood culture	
	IV treatment n=13	Oral treatment n=7	IV treatment n=6	Oral treatment n=6	IV treatment n=3	Oral treatment n=3	IV treatment n=5	Oral treatment n=5
Streptococci	7 (54%)	3 (43%)	2 (33%)	4 (66%)	2 (67%)	2 (67%)	0	0
E faecalis	2 (15%)	1 (14%)	0	0	0	0	3 (60%)	3 (60%)
S aureus	2 (15%)	2 (28%)	3 (50%)	1 (17%)	0	0	2 (40%)	1 (20%)
CNS	2 (15%)	1 (14%)	1 (17%)	1 (17%)	1 (33%)	1 (33%)	0	1 (20%)

IV; Intravenous.

Oral therapy versus OPAT- (HITH)

- Better adherence
- Less toxicity - linezolid
- Narrow and targeted therapy
- Interactions common- rifampicin

Table 514
Detailed description of side effect in treatment groups

Side effects	Intravenous treatment n=12	Oral treatment n=10
Gastro-intestinal symptoms, n (%)	0 (0)	3 (30.0)
Renal failure, n (%)	0 (0)	1 (10.0)
Hepatic failure, n (%)	0 (0)	1(10.0)
Bone marrow suppression, n (%)	2 (16.7)	4 (40.0)
Allergy, n (%)	10 (83.3)	1 (10.0)

The severity of the listed side effects necessitated shift of antibiotics in all cases. No further grading of side effects was registered. Side effects that did not necessitate shift of antibiotics were not registered.

INTERNAL MEDICINE JOURNAL RACP Specialists. Together

Original Article

Outpatient parenteral antimicrobial therapy is safe and effective for the treatment of infective endocarditis: a retrospective cohort study

A. K. F. Htin, N. D. Friedman, A. Hughes, D. P. O'Brien, S. Huffam, A.-M. Redden, E. Athan

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Conflict of interest: None.

Abstract

Background

Outpatient parenteral antibiotic therapy has been shown to be efficacious, safe and cost-

OPAT for IE

Aims: To evaluate the safety, efficacy and 1-year outcomes of patients with IE treated under HITH at our centre over 9 years.

Method: retrospective analysis of the clinical outcomes of all cases of IE treated with HITH at a tertiary referral centre was undertaken for patients treated between 2002-2011 (9 years).

Outcome measures included clinical cure, readmission rate, relapses and 1-year mortality

Results: 68 cases of IE were treated with HITH including 29 native valve infections, 24 prosthetic valve infections, 12 pacemaker lead infections, 1 defibrillator lead infection, 1 myocardial wall infection and 1 aortic graft infection. 13 cases had valve replacement surgery and 12 cases had removal of infected pacemaker leads.

S. aureus (18 cases), CNS (10 cases) and viridians-group streptococcus (18 cases) were the most common pathogens.

Median duration of antimicrobial therapy with HITH was 24 days (range 4 to 42 days). There were 3 readmissions during antimicrobial therapy with HITH. 2 patients relapsed. There were 2 deaths and one patient was lost to follow up.

One-year survival was 96% (65/68).

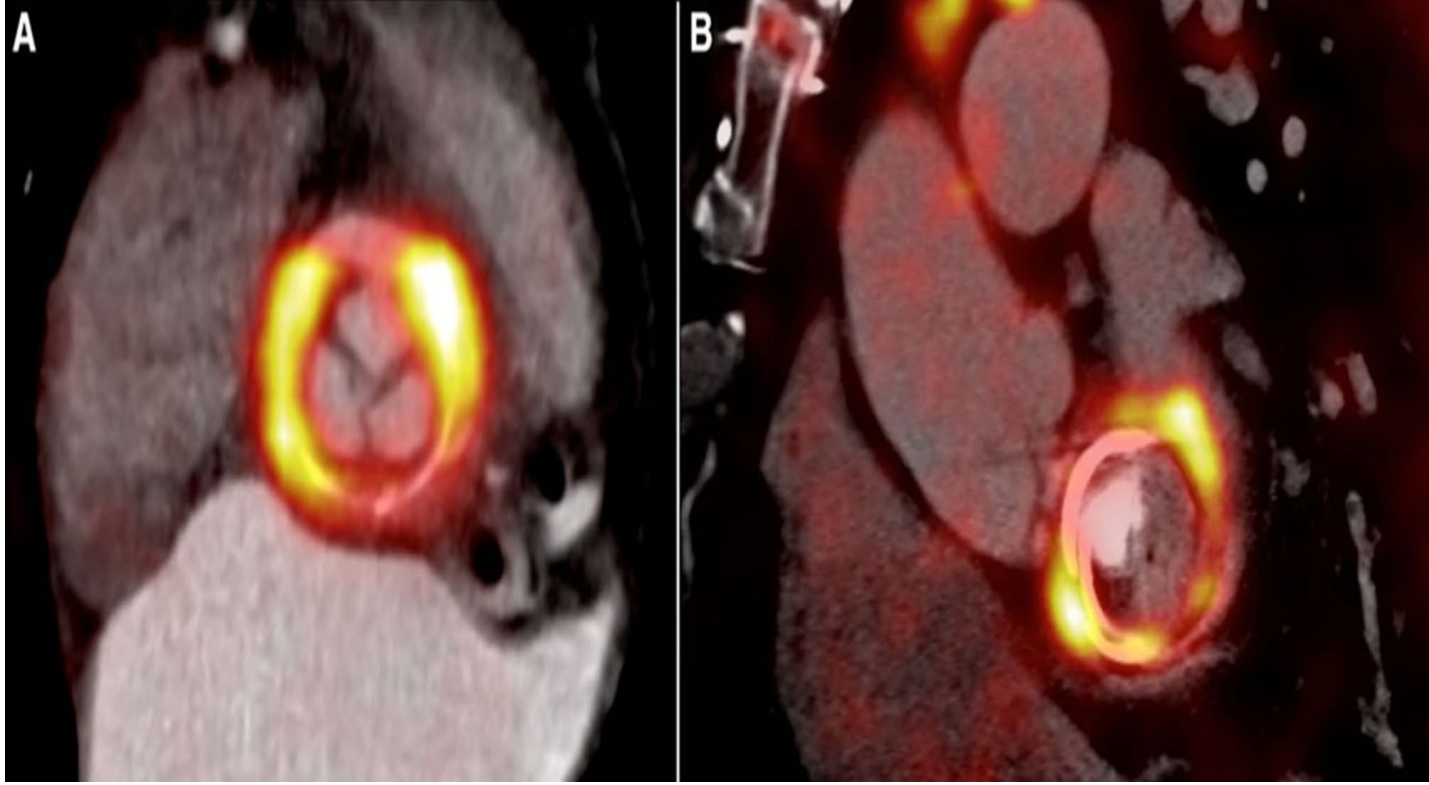
Conclusion: Outpatient antimicrobial therapy with HITH is safe and effective in carefully selected cases of IE.

Barwon Health Endocarditis service
March – May 2022

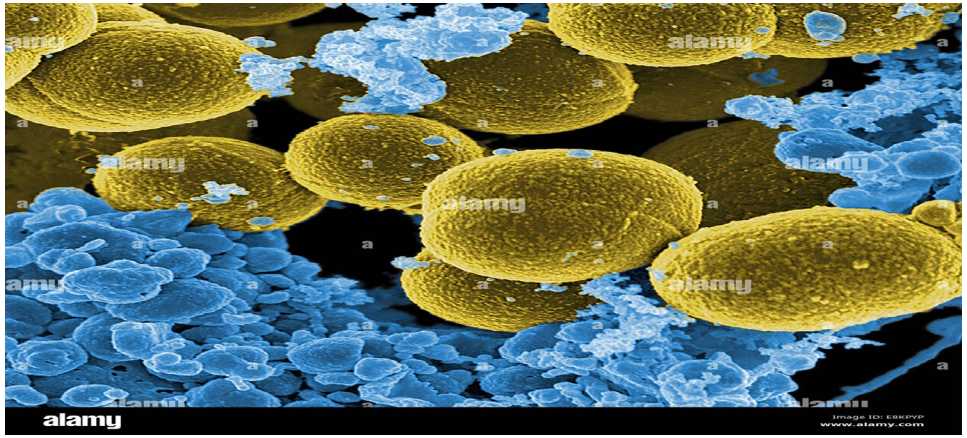
- 17 cases in 3 months
- Mean age 71 years
- *E fecalis* 8 cases - 3 PVIE, 3 surgery
- *S aureus* 4 cases - 2 surgery
- Enteric strep. 2 cases 1 CDIE
- Other 1 each Candida, CNS, HACEK

PVIE

- Small numbers 53 and 54
- Early surgery
- Few *S aureus* 11 cases

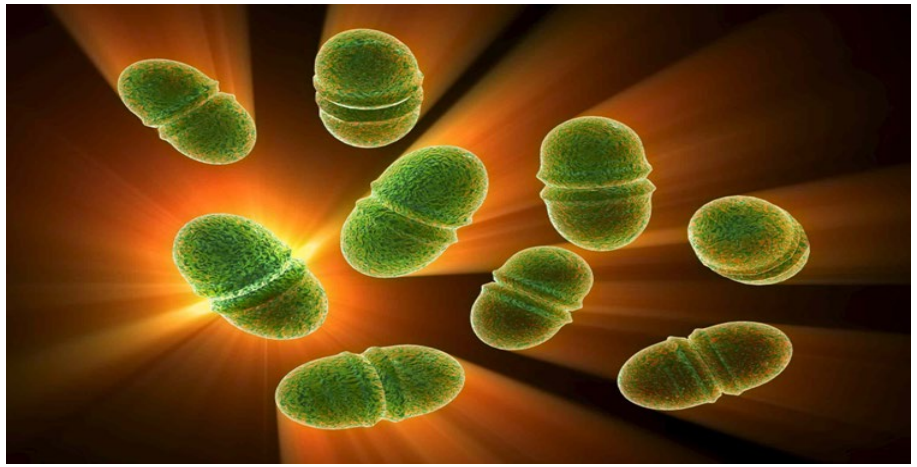


S aureus



- Small sample size
- High rates of early surgery
- No MRSA

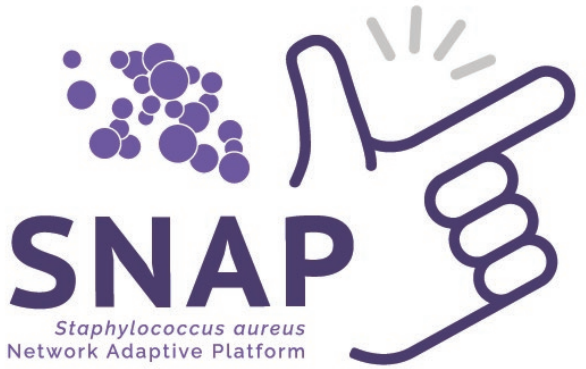
E fecalis



- Small sample size
- Low rates of HLAR
- High rates of surgery

Answer - POET 2 recruiting globally

- Shortened duration of parenteral therapy - 2 vs 4 weeks, 3 vs 6 weeks
- Include option of OPAT
- Larger cohort for outcomes of interest
- 12 month follow up
- Intention to treat analysis



The SNAP Trial

The *Staphylococcus aureus* Network Adaptive Platform Trial

Overview of the SNAP Trial

- SNAP aims to improve treatment outcomes for patients with *Staphylococcus aureus* bloodstream infections
- The SNAP Trial will include approximately 40 sites across Australia as well as sites in Canada, Israel, New Zealand, Singapore and the UK, and up to 7,000 patients.
- The study is coordinated by the Doherty Institute & The University of Melbourne
- The SNAP Trial will include adults, children, and pregnant women

Structure of the SNAP Domains

The SNAP Trial is split into 3 different treatment domains to answer the 3 questions below:

Antibiotic Backbone Domain

Which antibiotic is the best treatment to kill the Staph aureus bacteria?

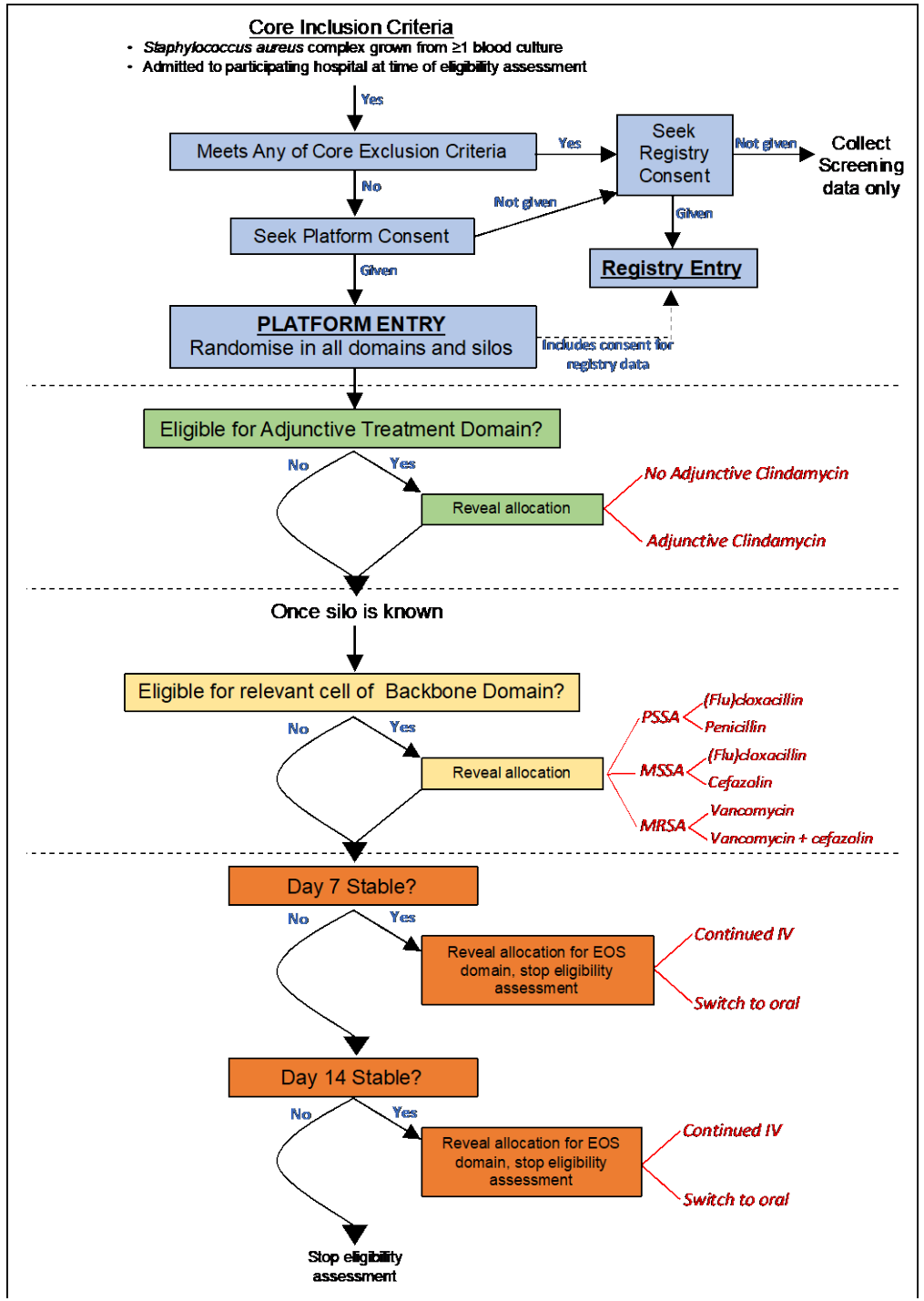
Adjunctive Treatment Domain

Will using an additional antibiotic help to improve outcomes of patients with SAB, by targeting the exotoxins?

Early Oral Switch Domain

Is it possible to switch from IV antibiotics to oral antibiotics part-way through the treatment without compromising patient outcomes?

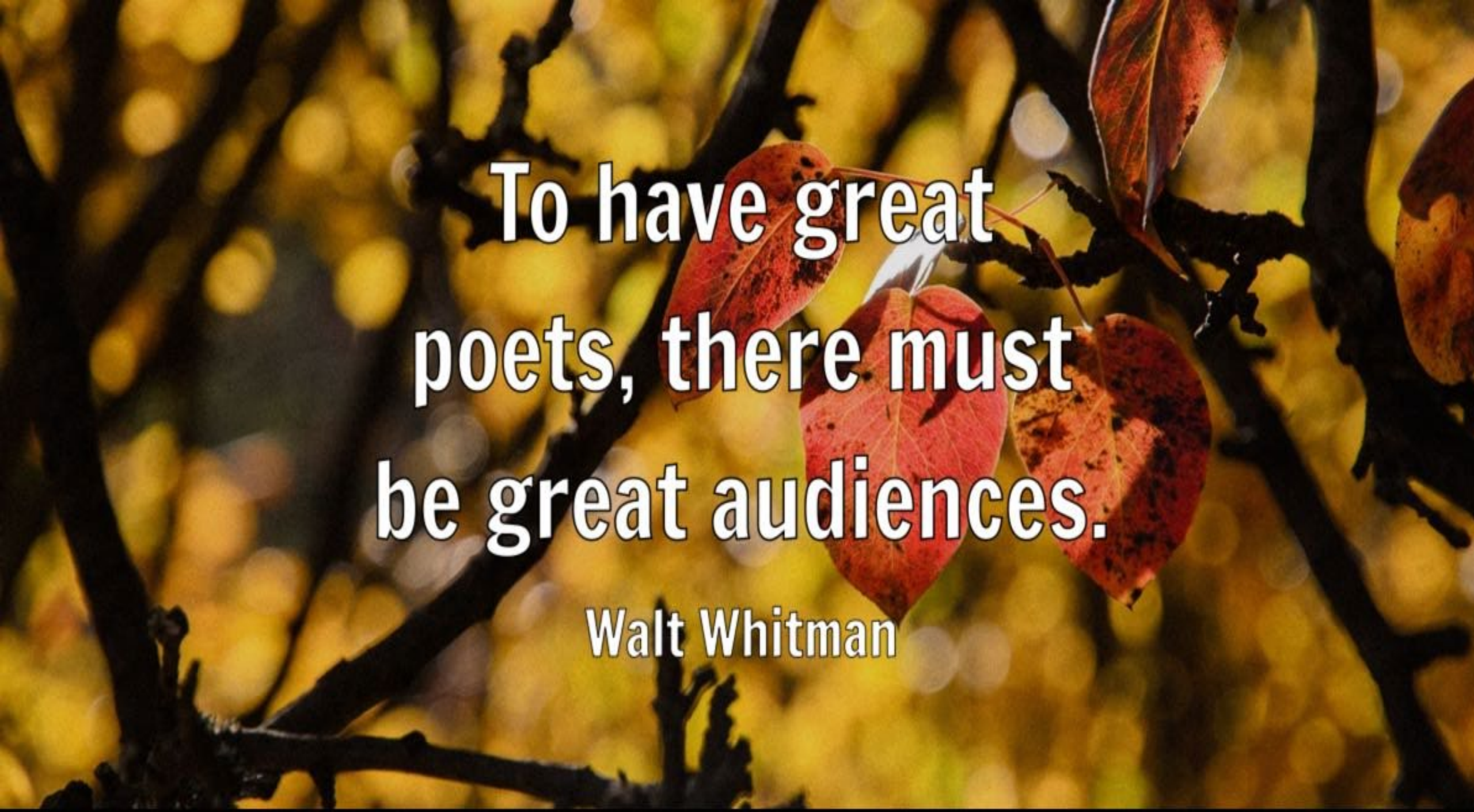
Silo	Antibiotic Backbone Domain	Adjunctive Treatment Domain	Early Oral Switch Domain
PSSA	(Flu)cloxacillin Penicillin	Clindamycin vs No clindamycin	<u>Stable at day 7</u> Switch to oral for or stay on IV for clinician-determined total duration <u>Stable at day 14</u> Switch to oral for or stay on IV for clinician-determined total duration
MSSA	(Flu)cloxacillin Cefazolin		
MRSA	Vancomycin vs Vancomycin plus cefazolin		



Patient Pathway Overview

For SNAP Platform Participants

- **Single consent discussion** (includes main trial, treatment domains & registry)
- Multiple **eligibility reveals** at specific timepoints
- **Ongoing assent** will be checked for participation in the EOS domain


To have great
poets, there must
be great audiences.
Walt Whitman