18 years

Data

Correlates

Experience

Creativity

Outpatient treatment of infective endocarditis

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background

- IE is a rare disease (4/100,000 population/Y)
- IE referral centers (often a cardiology department) are crowded with many critical patients
- The long hospital stay of IE patients contitutes a burden
- The outpatient parentral treatment (OPAT) is successfully used for other diseaes (dialysis, oncology, ..)
- Attempts of OPAT for lower risk IE has the potential to reduce cost and free some valuable hospital beds for more critical patients

barriers

- Unpredictable complications
- IV access care
- Access to urgent readmission
- Conditions at home
- … Medication cost

antibiotics

MDPI

Perspective

Outpatient Parenteral Antimicrobial Therapy for Infective Endocarditis—Model of Care

Dylan Rajaratnam [1] and Rohan Rajaratnam [1,2,3,*]

Antibiotics 2023, 12, 355.

Study	Study Location	Study Type	Number of IE Episodes	Mean age Male:Female *	Readmissions during Treatment	Mortality	Main Findings
Pajarón et al. 2015 [4]	Spain	Retrospective and prospective	48	63.1 34:11	6 (12.5%)	5 (10.4%) at 1 year	Self-administered OPAT is at least as effective in terms of efficacy and safety as healthcare-professional-administered OPAT.
Larioza et al. 2009 [5]	United States of America	Retrospective	43	N/A 29:14	10 (23.3%)	0 (0%) at 1 year	Patients completed at least 66% of their total treatment duration as outpatients after an inpatient stabilisation period (typically 1–2 weeks).
Lacroix et al. 2014 [11]	France	Retrospective	18	59.5 11:7	3 (16.7%)	1 (5.6%) at 3 months	OPAT in selected patients seems effective, safe and reduces costs by approximately EUR 15,000 per patient.
Cervera et al. 2011 [12]	Spain	Prospective	73	59.5 55:18	12 (16.4%)	3 (4.1%) at 1 year	OPAT for IE could be a safe and efficacious therapeutic option for carefully selected patients.
Partridge et al. 2012 [13]	United Kingdom	Retrospective	36	54.7 27:7	5 (13.9%)	1 (2.8%) at 30 months	OPAT is safe and effective in the management of IE, including for some patients who would have previously been considered high risk of complications (IDSA guidelines), such as those with infected prosthetic valves and *Staphylococcus aureus* IE.

Study	Study Location	Study Type	Number of IE Episodes	Mean age Male:Female *	Readmissions during Treatment	Mortality	Main Findings
Htin et al. 2013 [19]	Australia	Comparing the outcomes of patients with IE prior to (1996–2002) and after (2003–2009) the introduction of a formalised multidisciplinary OPAT team. Reveals a significant reduction in overall mortality.				(2.9%) at 1 year	OPAT in IE is safe and effective, including prosthetic valve infections and those who have undergone valve replacement surgery. Caution in patients with *Staphylococcus aureus* IE.
Chirillo et al. 2013 [20]	Italy					35 (34%) before and 31 (16%) after intervention of an OPAT team	Comparing the outcomes of patients with IE prior to (1996–2002) and after (2003–2009) the introduction of a formalised multidisciplinary OPAT team. Reveals a significant reduction in overall mortality.
McMahon et al. 2008 [21]	Australia	In selected patients, a shift from intravenously administered to orally administered antibiotic treatment was non-inferior to continued intravenous antibiotic treatment.				N/A	Hospital-in-the-home treatment is safe and effective. Caution in patient selection is required for *Staphylococcus aureus* IE.
Iversen et al. 2018 (POET trial) [22]	Denmark					0 (5%) at 6 months	In selected patients, a shift from intravenously administered to orally administered antibiotic treatment was non-inferior to continued intravenous antibiotic treatment.

General OPAT Criteria
- Adequate cognitive function and stable mental health
- Access to outpatient healthcare services (clinics/HITH)
- Access to transport if required
- Telephone access
- Ability of the healthcare system to provide daily review if required
Patient Criteria
- Absence of active illicit drug use
- Caution with high-risk patients (e.g., elderly, prosthetic endocarditis, multiple patient comorbidiities)
- Caution with high-risk culprit organisms (e.g., *Staphylococcal aureus*, *fungi* and *non-HACEK Gram-negative bacilli*)
- Absence of infective endocarditis complications (e.g., heart failure, renal failure, septic shock, neurological complications)
- Absence of treatment complications (e.g., adverse drug effects, diarrhoea, nausea, vomiting and catheter line infections)
- Stable intravenous access
- Absence of uncontrolled extra-cardiac foci of infection
Laboratory Criteria
- Decreasing inflammatory markers (neutrophil count, CRP)
- Stable renal function (GFR, creatinine) and hepatic function (LFTs, albumin, INR)

Electrocardiogram and Echocardiogram criteria
- Absence of conduction block (2nd and 3rd degree AV block)
- Decrease in size of the vegetation since starting in-hospital therapy
- Absence of para-valvular complications
- Vegetation ≤10 mm
Without Indications for Surgery
- Aortic or mitral IE with severe acute regurgitation causing refractory pulmonary oedema/shock
- Aortic or mitral IE with fistula into a cardiac chamber/pericardium causing refractory pulmonary oedema/shock
- Locally uncontrolled infection (e.g., abscess, false aneurysm, enlarging vegetation, persisting fever and positive blood culture for ≥10 days)
- Infection caused by fungi or multi-resistant microorganisms
- Prevention of embolism with a large vegetation >10 mm resulting in complications (embolic episode, heart failure, persistent infection, abscess)
- Prevention of embolism with a large vegetation >15 mm

HITH: hospital in the home; CRP: c-reactive protein; GFR: glomerular filtration rate; LFTs: liver function tests; INR: international normalised ratio; AV block: atrioventricular block.

Outpatient treatment of infective endocarditis

Clin Microbiol Infect 1998; 4: 3S47–3S55

*Patrick B. Francioli[1], Daniel Stamboulian[2], and the Endocarditis Working Group of the International Society of Chemotherapy**

Table 1 Risks associated with outpatient treatment of IE and measures to minimize them [2]

Risk	Measure
Sudden complications	Initiation of treatment in hospital
Delay in diagnosis of complications	Easy access to medical care if problems
	Selection of patients
Arterial embolism	Vegetations of <1 cm
Cardiac failure	Hemodynamically stable
Rupture of mycotic aneurysm	No symptoms suggestive of mycotic aneurysms
Problems with intravenous line	Prefer intermittent intravenous infusions or intramuscular injectio
	Intravenous therapy service
Hazards linked to activities requiring permanent attention	Avoidance (e.g. driving)
Compliance	Appropriate individual and social conditions

(early) exclusion criteria

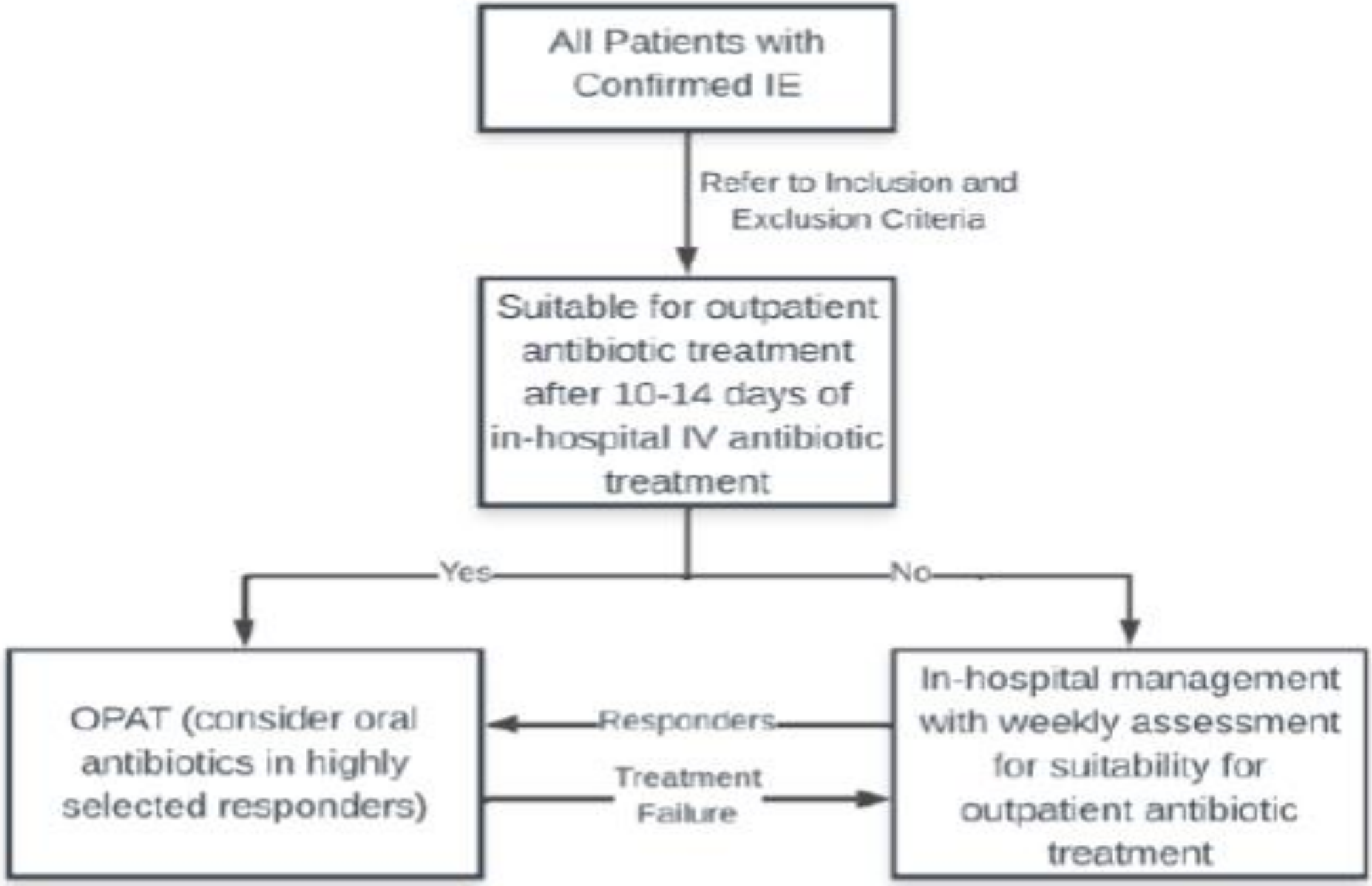
- Prosthetic valve endocarditis
- Complications
  - Embolism
  - Heart failure
  - Mycotic aneurysm
- Large vegetation
- Organism other than streptococci or HACEK
- Inappropriate conditions at home

Table 2. Proposed guidelines for the use of inpatient antibiotic therapy (IPAT) and outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis (IE).

Phase of treatment	Guidelines for use
Critical phase (weeks 0–2)	Complications of IE occur most frequently during this phase, and timely diagnosis is important for achieving optimal outcome. Preferred management: IPAT for 2 weeks. Exceptions: OPAT can be considered at 1 week for patients who meet the following 3 criteria: (1) infection with viridans streptococcal IE[a]; (2) medically stable condition without fever and with negative blood culture results, and stable electrocardiogram at time of proposed discharge; (3) no complications of IE and not in high-risk subgroup (see below).

Table 2. Proposed guidelines for the use of inpatient antibiotic therapy (IPAT) and outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis (IE).

Continuation phase (weeks 2–4 or 2–6)	Most patients who have not suffered complications of IE are likely to remain stable during the remainder of therapy, but side effects of parenteral antibiotic therapy may still occur. Preferred management: OPAT can be considered for the majority of patients who are medically stable (see above). Exceptions: IPAT should generally be continued for patients with any of the following characteristics: (1) complications of IE, such as congestive heart failure, conduction abnormality, mental status change, or evidence of perivalvular abscess on a transesophageal echocardiogram; (2) members of a high-risk subgroup: acute IE, aortic valve disease, prosthetic valve disease, or IE caused by *Staphylococcus aureus* or other virulent organisms.[b]


All Patients with Confirmed IE
Refer to Inclusion and Exclusion Criteria
Suitable for outpatient antibiotic treatment after 10-14 days of in-hospital IV antibiotic treatment
Yes
No
OPAT (consider oral antibiotics in highly selected responders)
Responders
Treatment Failure
In-hospital management with weekly assessment for suitability for outpatient antibiotic treatment

Outpatient intravenous treatment for infective endocarditis: safety, effectiveness and one-year outcomes.

- OPAT in 100 episodes.
  - Viridans streptococci in 34
  - Staphylococcus aureus in 27
  - Enterococci in 10.

- Adverse events in 27 episodes.
  - 24 due to IV lines, or drug reactions, change of treatment.
  - 3 serious adverse events
  - 5 further episodes of IE and 2 deaths.

J Infect. 2009 Dec;59(6):387-93

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Partial Oral versus Intravenous Antibiotic Treatment of Endocarditis

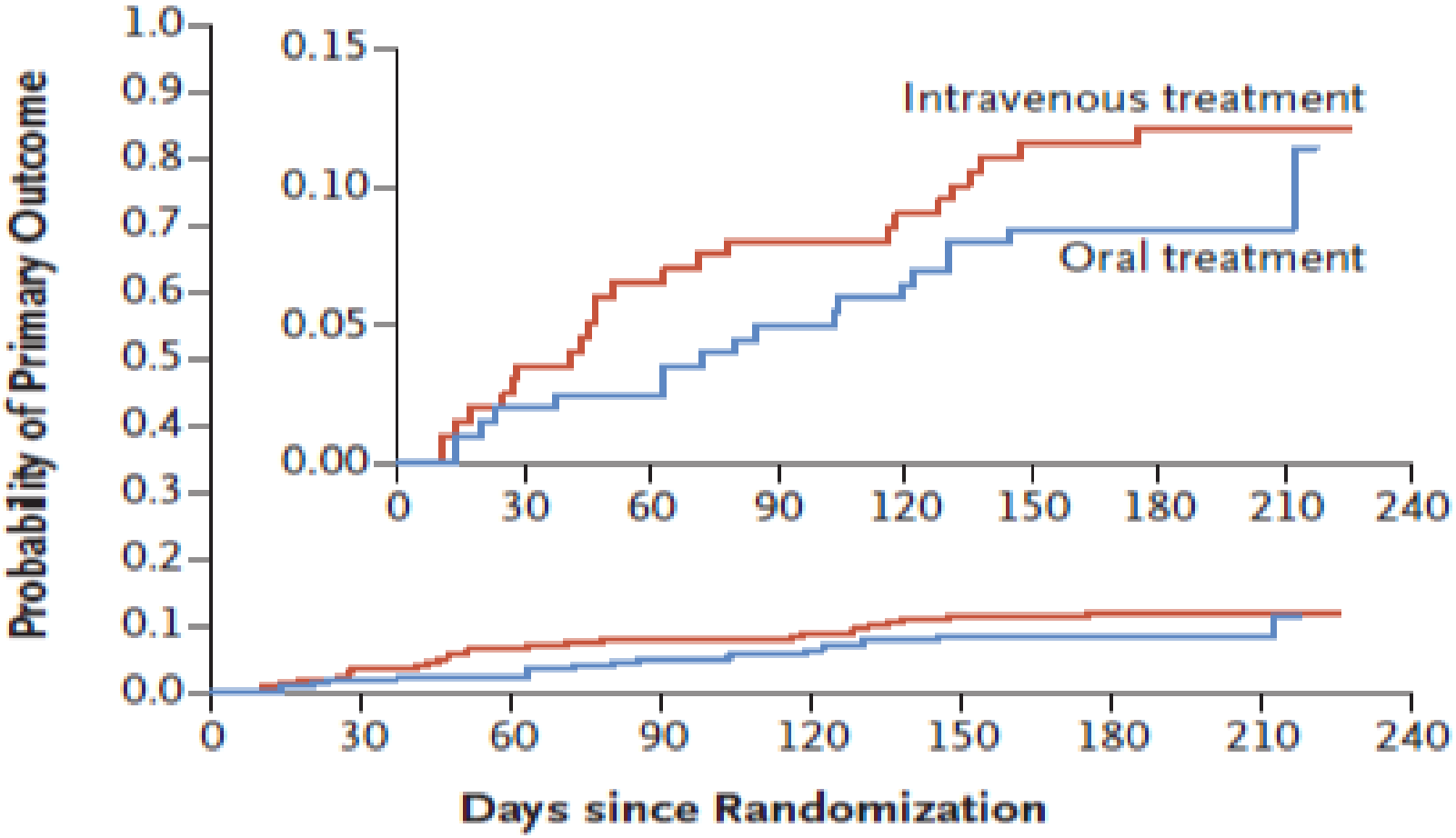
Baseline characteristics

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)

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)

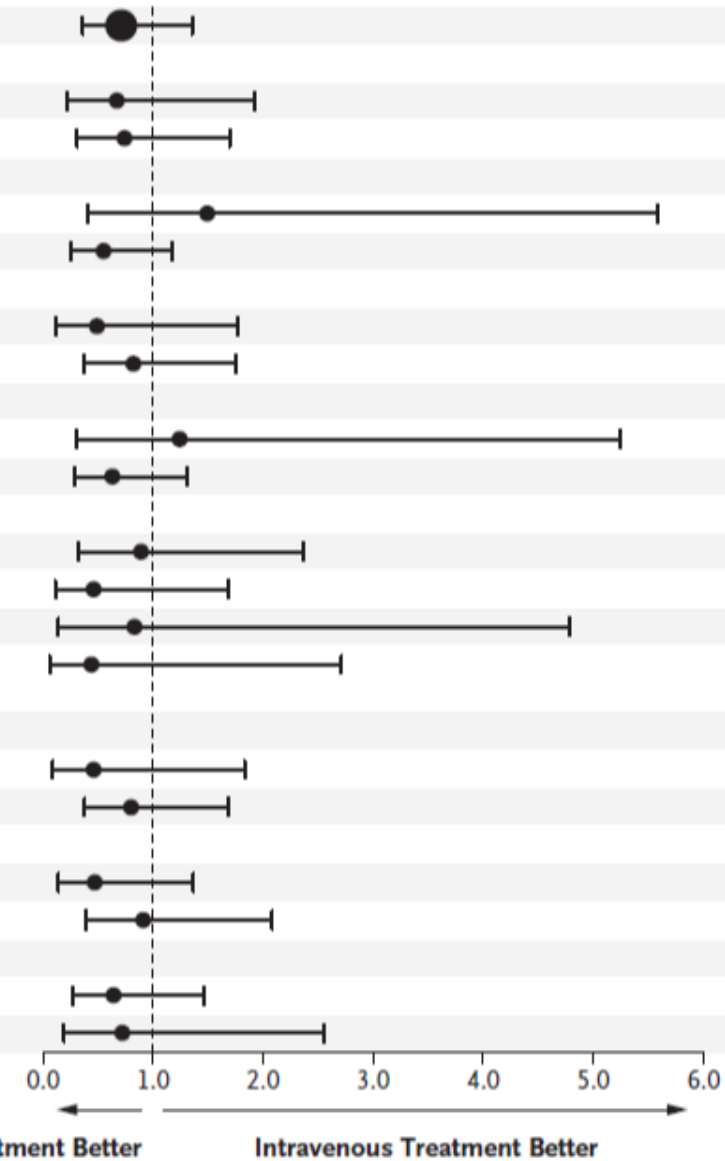
* Six patients, three in each group, had two outcomes.



No. at Risk									
Intravenous treatment	199	192	186	183	181	176	174	28	0
Oral treatment	201	197	196	191	188	184	183	36	0

Figure 2. Kaplan–Meier Plot of the Probability of the Primary Composite Outcome.

Subgroup	Intravenous Treatment	Oral Treatment	Odds Ratio (95% CI)	P Value for Interaction
	no. of events/total no. (%)			
All patients	24/199 (12.1)	18/201 (9.0)	0.72 (0.37–1.36)	
Age				0.34
≤65.5 yr	9/83 (10.8)	7/91 (7.7)	0.68 (0.23–1.93)	
>65.5 yr	15/116 (12.9)	11/110 (10.0)	0.75 (0.32–1.70)	
Sex				0.19
Female	5/50 (10.0)	6/42 (14.3)	1.50 (0.42–5.59)	
Male	19/149 (12.8)	12/159 (7.5)	0.56 (0.26–1.18)	
Diabetes				0.51
Yes	8/36 (22.2)	4/32 (12.5)	0.50 (0.12–1.78)	
No	16/163 (9.8)	14/169 (8.3)	0.83 (0.39–1.76)	
Renal disease				0.40
Yes	5/25 (20.0)	5/21 (23.8)	1.25 (0.31–5.24)	
No	19/174 (10.9)	13/180 (7.2)	0.64 (0.30–1.32)	
Bacteria				0.94
Streptococci	10/104 (9.6)	8/92 (8.7)	0.90 (0.33–2.37)	
Enterococcus faecalis	7/46 (15.2)	4/51 (7.8)	0.47 (0.12–1.69)	
Staphylococcus aureus	3/40 (7.5)	3/47 (6.4)	0.84 (0.15–4.78)	
Coagulase-negative staphylococci	4/10 (40.0)	3/13 (23.1)	0.45 (0.07–2.72)	
Surgical treatment			0.47 (0.10–1.84)	0.50
Yes	6/75 (8.0)	3/77 (3.9)	0.81 (0.39–1.69)	
No	18/124 (14.5)	15/124 (12.1)		
Type of valve			0.48 (0.15–1.37)	0.35
Prosthetic heart valve	11/53 (20.8)	6/54 (11.1)	0.92 (0.40–2.09)	
Native heart valve	13/146 (8.9)	12/146 (8.2)		
Involved valve			0.65 (0.28–1.47)	0.56
Aortic valve	16/109 (14.7)	11/109 (10.1)	0.73 (0.20–2.56)	
Mitral valve	6/65 (9.2)	5/72 (6.9)		



Methodology: oral antibiotic choice

Difficult to reproduce

1. Investigators developed oral AB regimens as part of the trial
2. AB with published data showing moderate to high bioavailability.
3. Regimens based on pharmacokinetic calculations and expected MIC for each species published by the European Committee on Antimicrobial Susceptibility Testing (EUCAST).
4. Susceptibility testing by disk diffusion was performed in accordance with EUCAST guidelines.
5. MICs determined with Etest or VITEK2, and the choice of AB adjusted accordingly.
6. Oral regimens consisted of 2 antibiotics from different classes with different antimicrobial mechanisms of action and different metabolization pathways (to reduce the risk of de facto monotherapy)

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

- Treatment algorithms requiring expert supervision and robust ID workforce.
- Treatment regimens not available in US (several agents with FDA warnings)
- Mandated frequent (2-3/W) outpatient visits
- Limited generalizability (only 20% of screened pts randomized)
- Conclusion:
  - Targeted oral therapy may have a role in the treatment of selected IE pts who have the health care infrastructure to support close monitoring.
  - At this time, it is premature to recommend a widespread early switch to oral therapy

summary

- At present, a sizable fraction of IE patients may be shifted to outpatient prentral antibiotic therapy (OPAT) provided that:

    1. They have streptococcal, HACEK, or MSSA disease
    2. They have been afebrile for at least 5D
    3. No prosthetic valve or intracardiac device
    4. No complications (embolic, cerebral, heart failure, renal failure ...)
    5. TEE shows no severe regurgitation, ring abscess, or long mobile veg.
    6. Home facilities for IV therapy and care of venous access
    7. Twice weely outpatient visits (living near hospital)
    8. Immediate access to re-admission if needed

- Outpatient oral therapy is an atractive idea whos time has not come