Background and Overview

Citation	Freling S, Wald-Dickler N, Banerjee J, et al. Real-world Application of Oral Therapy for Infective Endocarditis: A Multicenter Retrospective, Cohort Study. Clinical Infectious Diseases. Published online March 7, 2023:ciad119. doi:10.1093/cid/ciad119
Background	• Infective endocarditis (IE) is an uncommon infectious syndrome with an estimated incidence of 11-15 cases per 100,000 people[1] • Increased risk: age > 60 years, male sex, intravenous (IV) drug use, structural heart disease[2] • Associated with significant morbidity and mortality • Current guidelines published in 2015 by the American Heart Association and endorsed by the Infectious Diseases Society of America primarily recommend IV antibiotics for the entire treatment duration[3]

Previous Studies	Trial	Methods	Treatment	Results
	Stamboulian et al., 1991[4]	• Open label, prospective, randomized trial • IE due to penicillin susceptible Streptococci • 30 patients total	• 4 weeks of ceftriaxone (CRO) • 2 weeks of ceftriaxone followed by 2 weeks of amoxicillin (AMX)	• Clinical cure: 15 CRO vs. 15 AMX • Complications: 1 CRO vs. 1 AMX • All patients achieved bacteriologic cure
	Heldman et al., 1996[5]	• Open label, prospective, randomized trial • Patients with right-sided staphylococcal IE and known injection drug use • 93 patients randomized, 44 patients total	• Oral (PO): 5 days of IV antibiotics followed by ciprofloxacin + rifampin • IV: (oxacillin or vancomycin) + gentamicin	• Treatment failure: 5.2% PO vs. 12% IV (p=0.6) • Adverse effects: 3% PO vs. 62% IV (p<0.001)
	Iversen et al., 2019[6]	• Randomized, noninferiority, multicenter trial • Patients with left-sided IE • 400 patients total	• PO: (amoxicillin, linezolid, dicloxacillin, or moxifloxacin) + (rifampin, fusidic acid, or moxifloxacin) • IV: according to European Society of Cardiology guidelines	• Composite of mortality, surgery, embolic events, or bacteremia relapse at 6 months: 9% PO vs 12.1% IV (p=0.4) • Composite at 5 years: 32.8% PO vs. 45.2% IV (HR 0.65, 95% CI 0.47-0.9) • Adverse effects: 5% PO vs. 6% IV (p=0.66)

Methods

Objective	To compare outcomes of patients with IE treated with oral transitional therapy compared to IV-only therapy
Study Design	• Multicenter retrospective cohort study • 3 academic, acute care, safety net hospitals in California funded by Los Angeles County • December 2018 – June 2022
Intervention	Clinical criteria for oral transitional therapy: • Clinically stable with no immediate indication for cardiac surgery • Clearance of bacteremia • No concerns regarding absorption or psychosocial issues • Oral antibiotic regimen available based on *in vitro* susceptibilities and clinical data (options included amoxicillin, dicloxacillin, levofloxacin, moxifloxacin, trimethoprim-sulfamethoxazole, linezolid, rifampin) Patients were assigned to the IV or oral cohort based on what antibiotic route they received at hospital discharge

<table>
<tr><td>Study Population</td><td>
<u>Inclusion Criteria</u>
• Blood culture positive for:
  ○ Staphylococcus species
  ○ Streptococcus species
  ○ Enterococcus species
  ○ HACEK organisms (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, and Kingella)
• Definite or probable IE

<u>Exclusion Criteria</u>
• <18 years of age
• Inadequate documentation
• Died prior to receiving 14 days of treatment
• Blood culture was non-clinical or from an autopsy
• Blood culture was obtained from the ED or outpatient without follow-up
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<tr><td>Study Outcomes</td><td>
<u>Primary outcome</u>
• Clinical success at 90 days: defined as being alive, without recurrent bacteremia, and without treatment-emergent infectious complications

<u>Secondary outcomes</u>
• Clinical success at last follow-up
• Treatment-related adverse events
• Hospital length of stay
• Hospital readmission rates
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<tr><td>Statistical Analysis</td><td>
• Continuous variables were compared using nonparametric Mann-Whitney Unpaired Test
• Dichotomous variables were compared using Chi-squared or Fisher exact tests
• Multivariable logistic regression was conducted for outcomes of clinical success at 90 days and last follow-up
• Adjusted odds ratios for primary outcomes were calculated with Wald 95% confidence intervals
• Alpha = 0.05
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<tr><td colspan="2">Results</td></tr>
<tr><td>Baseline Demographics</td><td>
• 3968 patients with positive blood cultures were identified, of whom 257 were included
• The tricuspid valve was most common valve affected in the PO group while the aortic valve was most commonly affected in the IV group
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Characteristic	IV (n=211)	PO (n=46)	p value
Age, median (IQR)	55 (42-65)	39 (31-62)	**0.01**
Hispanic Race, n (%)	129 (61.1%)	29 (63%)	0.18
Male, n (%)	152 (72%)	32 (69.6%)	0.22
Diabetes Mellitus, n (%)	75 (35.5%)	9 (19.6%)	**0.04**
Dialysis Dependence, n (%)	42 (19.9%)	1 (2.2%)	**0.001**
Injection Drug Use, n (%)	38 (18%)	17 (37%)	**0.01**
Definite IE, n (%)	128 (60.7%)	28 (60.9%)	0.98
Prosthetic Valve, n (%)	31 (14.7%)	4 (8.7%)	0.28
Time to Last Follow-Up, median (IQR)	204 (51-495)	93.5 (26-279)	**0.02**

Pathogens	IV (n=211)	PO (n=46)	p value
S. aureus	110 (52.1%)	29 (63%)	0.18
MSSA	67 (31.8%)	13 (28.3%)	0.64
MRSA	43 (20.4%)	16 (34.8%)	**0.04**
***Streptococcus* species**	57 (28.4%)	10 (21.7%)	0.46
E. faecalis	29 (13.7%)	4 (8.7%)	0.25

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<tr><td>Treatment Characteristics</td><td>
• Oral regimens
  ○ Linezolid based regimen: 65.2%
  ○ High dose penicillin based regimen: 17.4%
  ○ Fluoroquinolone based regimen: 13%
  ○ Trimethoprim-sulfamethoxazole based regimen: 4.3%
• Median total duration: 42 days in both groups
• Median duration of IV lead in in PO group: 15.5 days
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Results

Table 1. Primary Outcome

Outcome n (%)	IV (n = 211)	PO (n = 46)	p Value
Clinical Success at 90 Days	178 (84.4%)	40 (87%)	0.66
Alive	193 (91.5%)	41 (89.1%)	0.61
Lack of Recurrence of Bacteremia	204 (96.7%)	45 (97.8%)	0.69
Absence of Treatment-Emergent Complications	185 (87.7%)	44 (95.7%)	0.12

Table 2. Secondary Outcomes

Outcome	IV (n = 211)	PO (n = 46)	p Value
Clinical Success at Last Follow-Up, n (%)	173 (82%)	35 (76.1%)	0.36
Length of Stay, median (IQR)	16 (10-31)	14.5 (8.8-23.3)	0.2
Readmission within 90 days, n (%)	72 (34.1%)	12 (26.1%)	0.29

Table 3. Adverse Events

Outcome n (%)	IV (n = 211)	PO (n = 46)	p Value
Total Adverse Events	58 (27.5%)	4 (8.7%)	**0.004**
AKI	23 (10.9%)	1 (2.2%)	**0.048**
Line Related Complications	17 (8.1%)	0 (0%)	**0.04**
Cytopenia	10 (4.7%)	2 (4.3%)	0.66

Discussion & Conclusion

Authors Conclusions

- Using rational clinical criteria, it is possible to select patients with IE that can be safely treated with oral therapy, including patients with MRSA infections
- Oral therapy leads to similar success rates as IV-only therapy but with significantly fewer adverse effects

Critique

Strengths

- Practical oral regimens and criteria for oral treatment
- High proportion of MRSA infections
- Inclusion of prosthetic valve IE and patients who use IV drugs

Weaknesses

- Retrospective nature
- Imbalance in baseline characteristics
- Small oral group
- Predominantly Hispanic population
- IV regimens not reported

Conclusions

These findings support those of previous randomized controlled trials showing that transition to oral therapy is noninferior to IV for the treatment of IE. There are several oral agents that offer safe alternatives, including linezolid, and the balance of benefits versus risks often falls in favor of oral antibiotics.

References

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Teaching Point

"Real World Data"	• Randomized controlled trials (RCTs) are considered the gold standard of study design • Real world data refers to data collected from diversified areas of daily life that are outside of the scope of tightly regulated randomized controlled trials <u>Disadvantages</u> • Possible incomplete data • Consistency in treatment • Unable to evaluate new therapy • Potential for bias <u>Advantages</u> • Easier to conduct • Larger and more heterogenous populations • Matches challenges of clinical practice Real world data cannot replace RCTs, but these two can have a complementary relationship