Oral Antibiotics for Native Valve Infective Endocarditis: Is PO a Go?

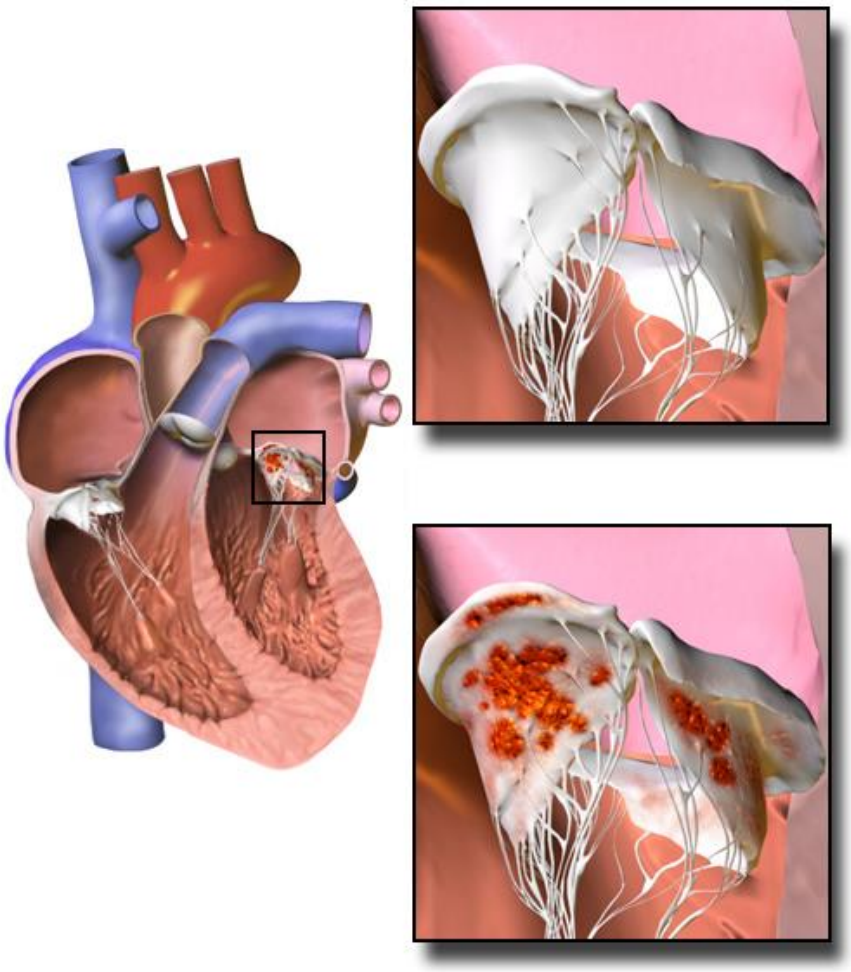

Figure 1. Infective endocarditis[1]

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Learning Objectives

Pharmacists

1. Identify common pathogens that contribute to the development of infective endocarditis.
2. Evaluate the evidence supporting the use of oral antibiotics in the treatment of native valve infective endocarditis.
3. Assess a patient with native valve infective endocarditis and determine if the use of oral antibiotics is appropriate.

Technicians

1. List common pathogens that contribute to the development of infective endocarditis.
2. Explain why antibiotics are generally given intravenously to treat infective endocarditis.
3. Identify a patient with native valve endocarditis who may benefit from the use of oral antibiotics.

Abbreviations

AHA: American Heart Association	IQR: interquartile range
BID: twice daily	IV: intravenous
BMI: body mass index	IVU/IVDU: intravenous drug use
CHF: congestive heart failure	LOS: length of stay
CIED: cardiac implantable electronic device	MDR: multidrug resistant
CIED-IE: cardiac implantable electronic device-related infective endocarditis	MIC: minimum inhibitory concentration
CKD: chronic kidney disease	MSSA: methicillin resistant *S. aureus*
CNS: central nervous system	MSSA: methicillin susceptible *S. aureus*
CONS: coagulase-negative staphylococci	NVIE: native valve infective endocarditis
CRP: C-reactive protein	PD: pharmacodynamic
CV: cardiovascular	PICC: peripherally inserted central catheter
DM: diabetes mellitus	PK: pharmacokinetic
DS: double strength	PO: oral, by mouth
DVT: deep vein thrombosis	PVIE: prosthetic valve infective endocarditis
ECG: electrocardiogram	QID: four times daily
ESC: European Society of Cardiology	SCr: serum creatinine
ESR: erythrocyte sedimentation rate	s/p: status post
IE: infective endocarditis	T&C: trimethoprim-sulfamethoxazole + clindamycin
GI: gastrointestinal	TEE: transesophageal echocardiogram
GU: genitourinary	TID: three times daily
HD: hemodialysis	TMP-SMX: trimethoprim-sulfamethoxazole
HF: heart failure	TTE: transthoracic echocardiogram
IDSA: Infectious Diseases Society of America	VGS: Viridans group streptococci
IM: intramuscular	WBC: white blood cells

Introduction

- Infective endocarditis (IE): inflammation of the endocardium due to bacterial (or rarely fungal) infection[2,3]
    - Typically affects native heart valves, but may involve nonvalvular areas or implanted materials (e.g., prosthetic heart valves, cardiac implantable electronic devices [CIEDs])

Epidemiology and Etiology

- IE relatively uncommon, but prevalence has increased since 2000 with 2-15 cases per 100,000 person-years in the United States[4,5]
- Mean male-to-female ratio: 2:1[6]

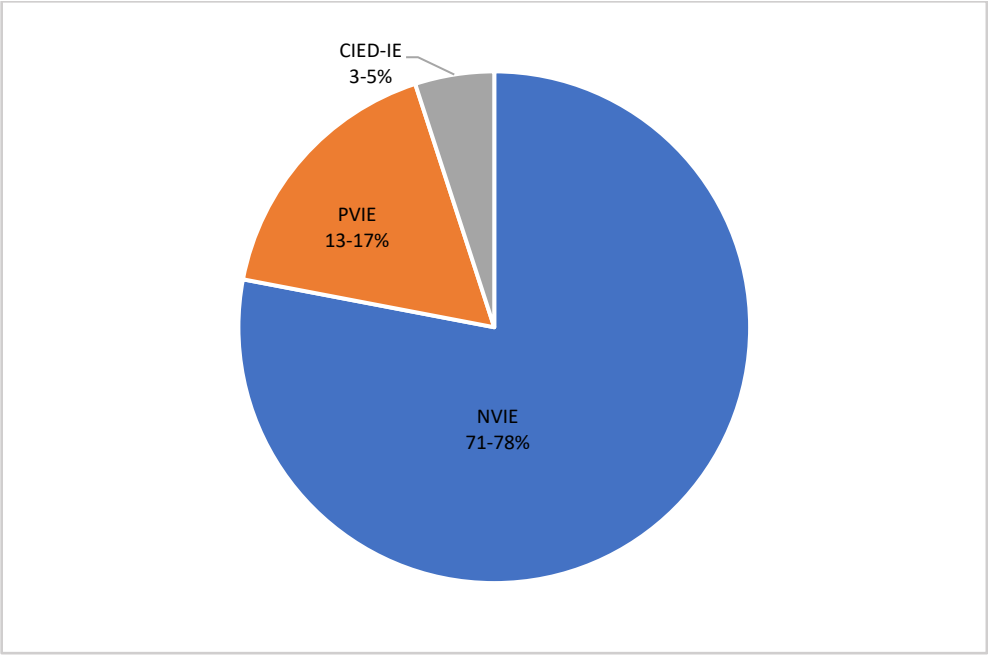


Figure 2. IE Classification by Site of Infection[8,10,11]

Table 1. Risk Factors for IE[6-11]	
Presence of a prosthetic valve (highest risk)	Acquired valvular dysfunction
Previous IE (highest risk)	CIEDs
Healthcare-related exposure (high risk)	Chronic heart failure
Congenital heart disease	Mitral valve prolapse with regurgitation
Advanced age	IVDU
Chronic IV access	HIV infection
Diabetes mellitus (DM)	Poor dentition and/or oral hygiene

Microbiology

- Most common causative pathogens: staphylococci, streptococci, and enterococci[8,10,12]
    - Staphylococci: increased prevalence due to emergence of healthcare-associated IE
        - Common in IVDU
    - Streptococci: associated with dental procedures/poor oral hygiene (particularly VGS)
        - Prevalence decreasing
    - Enterococci: associated with GI/GU surgery[13]

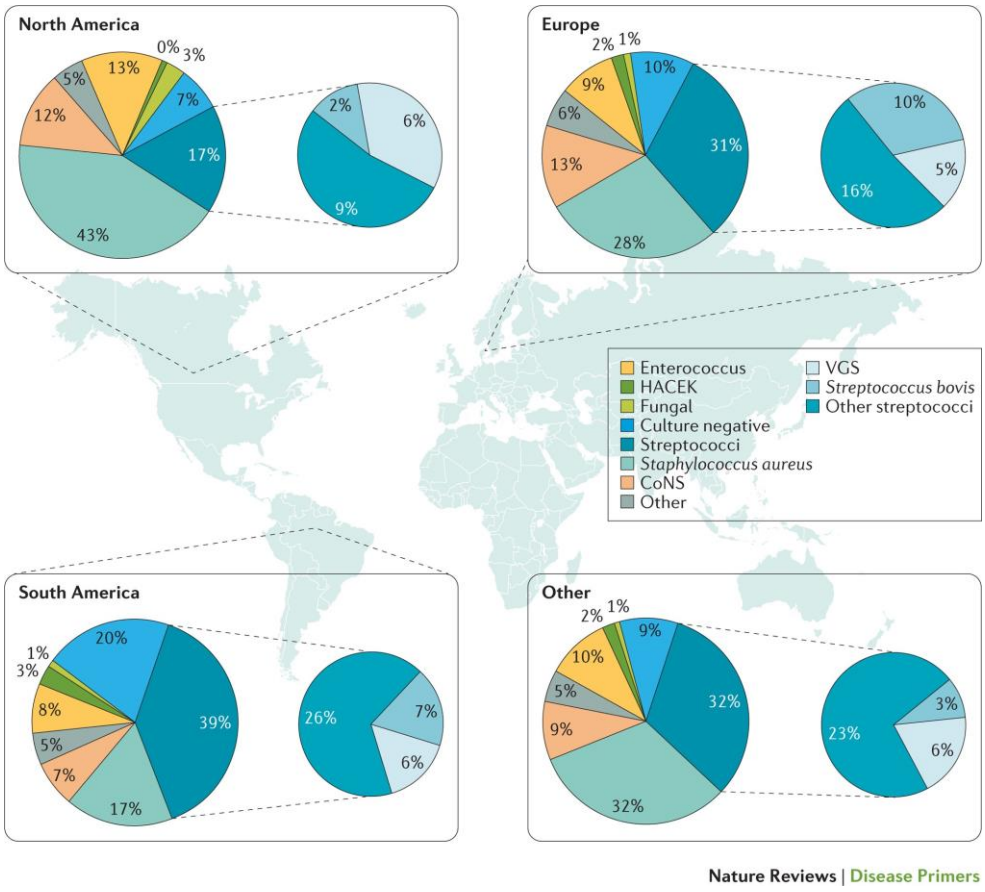


Figure 3. Global Epidemiology of Causative Pathogens Involved in IE[14]

Valve Involvement

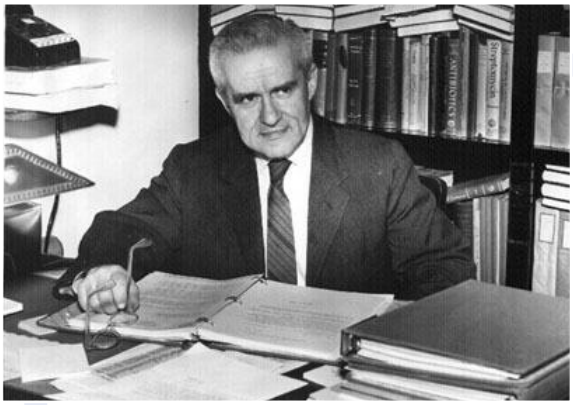
- Aortic and mitral valves most affected in IE
- Tricuspid valve IE less common
    - Generally associated with IVDU
- Pulmonic valve infection rare[12,13]

Left- vs Right-Sided Disease

- Left: morbidity and mortality high despite improvements in early recognition and treatment[15-17]
    - In-hospital mortality ranges from 15 to 45%
    - Cardiac valve surgery required in 50% of patients
- Right: mortality rate <15%[10]

The IV-Only Dogma

- Experts have asserted for decades that treatment of IE requires prolonged therapy consisting of IV antibiotics[18]
    - Dogma developed when penicillin was most effective treatment for IE
    - Penicillin administered IV only as its PO absorption considered unreliable
    - Concern about penetrating vegetations on heart valves
- History of antibiotic use to treat IE
    - Mid-1930s: sulfonamides developed
        - Disappointing results in IE, with mortality rates of 96%, as compared to >99% prior to antibiotics[19-20]
    - 1940s: IV penicillin G available
        - Cure rates rise to 85%[21]
    - Late 1940s/early 1950s: tetracyclines and macrolides developed
        - Cure rates <30%[22]
    - Mid-1950s: PO formulations of penicillin available
        - Not regarded as adequate for treatment of IE due to concerns about bioavailability and past failures[21,22]



Maxwell Finland: American scientist, medical rearcher, and expert on infectious diseases

"In this disease, oral administration... has generally been discarded as inadequate. Presumably, the oral route is at times successful... it is more likely, however, that such usage is responsible for many therapeutic failures... However, little of this type of experience is recorded, and therefore this assumption cannot be authenticated." (1954)

Figure 4: Early Opposition to PO Antibiotics in IE[21-23]

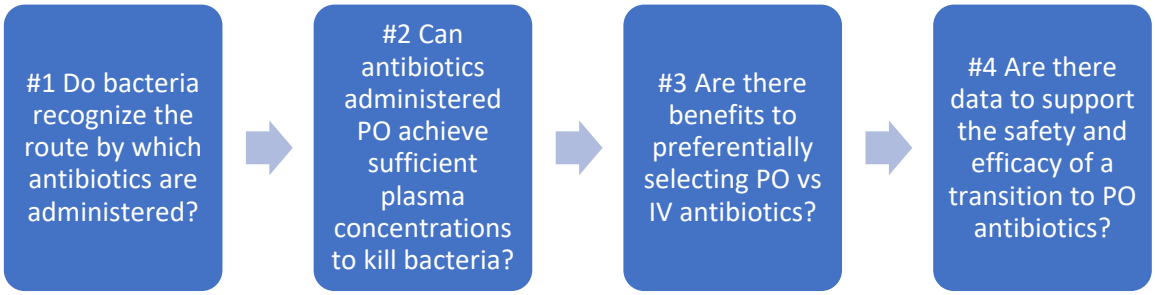
Present Day: Review of Guidelines

Table 2. Guideline Recommendations and Supportive Commentary Regarding the Use of PO Antibiotics in IE

Organization	Recommendations	Supportive Commentary
AHA/IDSA (2015)[10]	• Proposed treatment for IE due to MDR *Enterococcus* spp. (IIb, C): linezolid 600 mg IV or PO every 12 hours x >6 weeks	• "Cure rates for right-sided *S aureus* IE in IDUs are high (>85%) and may be achieved with relatively short courses of

	○ May be associated with potentially severe bone marrow suppression, neuropathy, and numerous drug interactions ○ Cardiac valve replacement may be necessary for cure	either parenteral or oral treatment (2-4 weeks)." • "In patients for whom parenteral antibiotic therapy is problematic, oral treatment may be a reasonable option. Two studies have evaluated the use of predominately oral 4-week regimens (featuring ciprofloxacin plus rifampin) for the therapy of uncomplicated right-sided MSSA IE in IDUs. In each study… cure rates were >90%. However, the relatively high rate of quinolone resistance among contemporary *S aureus* strains has made this alternative treatment strategy problematic."
ESC (2015)[9]	• Alternative regimen for native valve IE (NVIE) due to MSSA (IIb, C) and as an alternative regimen for NVIE in MRSA or in penicillin-allergic patients (IIb, C): trimethoprim-sulfamethoxazole (TMP-SMX) 960 mg/4800 mg/day (in 4-6 divided doses) IV x1 week, then PO x5 weeks + clindamycin 1800 mg/day (in 3 divided doses) x1 week • Proposed regimen for IE due to MDR *Enterococcus* spp. (IIa, C): linezolid 2 x 600 mg/day IV or PO every 12 hours x ≥8 weeks ○ Monitor hematological toxicity	• "Short-term (2-week) and oral treatments have been proposed for uncomplicated right-sided native valve MSSA IE, but these regimens cannot be applied to left-sided IE." • IE due to HACEK-related species: "Ciprofloxacin (400 mg/8-12 h IV or 750 mg/12 h PO) is a less well-validated alternative." • PO regimens proposed for antibiotic treatment of blood culture-negative IE • "Alternatively, when conventional IV route therapy is not possible, right-sided *S. aureus* IE in IVDUs may also be treated with oral ciprofloxacin (750 mg twice daily) plus rifampicin (300 mg twice daily) provided that the strain is fully susceptible to both drugs, the case is uncomplicated and patient adherence is monitored carefully."

Contextual Framework for Evaluating a Transition to PO Antibiotics



Question #1

- Aside from reliability in delivering drugs to the bloodstream, there is nothing innately superior about IV route
- Bacteria have no way of detecting which route was selected, nor do they respond any differently to the drug based on how it was delivered

Question #2

- Antibiotics must achieve adequate plasma concentrations to kill the offending pathogen (peak blood level:MIC_{90} ≥1)
    - Older tetracyclines, macrolides, and sulfonamides fail to achieve therapeutic concentrations
    - Penicillin and others that followed achieve concentrations that exceed the minimum inhibitory concentration
- Other PD parameters also relevant (e.g., time above MIC_{90} for beta lactams, total 24-h exposure/MIC_{90} for most other agents)

Table 3. Peak Blood Levels vs MICs Achieved by Antibiotics Used to Treat IE in Published Studies[18]

PO drug	Peak blood level (µg/mL)	MIC_{90} (µg/mL)	Peak blood level:MIC_{90}
Erythromycin, 500 mg	0.5	≥4	0.125
Tetracycline, 250 mg	1	≥4	0.125
Sulfanilamide, 4000 mg	50	50-70	0.8
Moxifloxacin, 400 mg, for *S. aureus*	4	4	1
Levofloxacin 750 mg, for *Staphylococcus* spp.	9	4	2.25
Clindamycin 600 mg, for *Staphylococcus* spp.	10	2	5
Penicillin V, 500 mg, for *Streptococcus* spp.	5	1	5
Rifampin, 600 mg, for gram-positive cocci	7	1	7
Linezolid, 600 mg, for gram-positive cocci	15	2	7.5
Amoxicillin, 1000 mg, for *Streptococcus* spp.	10	1	10
Moxifloxacin, 400 mg, for *Streptococcus* spp.	4	0.25	16
TMP-SMX, 320 mg/1600 mg, for *Staphylococcus* spp.	100	4.75	22

Question #3

- Taking medications PO avoids route-specific complications associated with prolonged IV access, including potentially severe adverse effects[24-27]
    - DVT: 5-15% for hospitalized patients vs 2-5% for ambulatory patients
    - Central line infection: 2.1 per 1,000 catheter days in hospitalized patients vs 1.0 per 1,000 catheter days in ambulatory patients
    - Catheter occlusion: 2.4-6% for hospitalized patients vs 4.5-7.4% for ambulatory patients
    - Accidental withdrawal of catheter: 8.9%, hospitalized older adults primarily
- Convenience[28]
    - Over 60% of patients report signs or symptoms of a possible complication or adverse effect after PICC placement
    - 1:4 patients report restrictions in activities of daily living

- Cost savings
    - Reduced medication and labor costs associated with PO route

Question #4

Table 4. Early Observational Studies of PO Antibiotic Therapy for IE[29]

Reference	Cases	Design	Microbiology	Therapy	Cure
Schein et al (1948)[30]	81 NVIE (right- vs left-sided not specified)	Retrospective	Streptococci (94%) *S. aureus* (1%) Enterococci (1%) *H. influenzae* (4%)	PO sulfonamides (sulfanilamide, sulfapyridine, sulfathiazole, or sulfadiazine) x10 days to 14 weeks	10%
Friedberg et al (1952)[31]	11 NVIE (right- vs left-sided not specified)	Retrospective	VGS (55%) *E. faecalis* (18%) Culture negative (27%)	PO aureomycin x5 to 8 weeks	36%
Campeau et al (1963)[32]	10 NVIE (right- vs left-sided not specified)	Retrospective	VGS (60%) *E. faecalis* (30%) Anaerobic bacteria (10%)	PO phenithicillin x4 to 6 weeks (IM streptomycin x2 weeks in 6 cases, concomitant probenecid in 2 cases)	80%
Gray et al (1964)[33]	13 NVIE (right- vs left-sided not specified)	Retrospective	VGS (69%) *E. faecalis* (16%) Culture negative (15%)	PO ampicillin or propicillin ± probenecid x6 weeks	92%
Phillips et al (1977)[34]	13 NVIE (right- vs left-sided not specified, children)	Retrospective	VGS (62%) Staphylococci (23%) Other streptococci or enterococci (15%)	IV therapy x<2 weeks (92% ≤3 days), then PO penicillin V, ampicillin, cloxacillin, flucloxacillin, or erythromycin x4 to 6 weeks)	100%
Pinchas et al (1983)[35]	11 NVIE (left-sided, uncomp-licated)	Prospective	VGS (100%)	PO ampicillin (high dose) x6 weeks + probenecid x4 weeks + IM streptomycin x2 weeks	90%
Chetty et al (1988)[36]	15 NVIE (right- vs left-sided not specified, uncomp-licated)	Prospective	Streptococci (60%) Culture negative (40%)	PO amoxicillin (high dose) ± probenecid x6 weeks	87%

Dworkin et al (1989)[37]	13 IVDUs with NVIE (right-sided)	Prospective	*S. aureus* (100%)	IV ciprofloxacin + PO rifampin x1 week, then PO ciprofloxacin + PO rifampin x3 weeks	77%
Colli et al (2007)[38]	12 NVIE and 2 PVIE (left-sided)	Retrospective	MRSA (57%) VGS (29%) *E. faecalis* (14%)	IV vancomycin x5 days (average), then PO linezolid x3 weeks	100%

Table 5. Stamboulian D, Bonvehi P, Arevalo C, et al. Antibiotic management of outpatients with endocarditis due to penicillin-susceptible streptococci. *Rev Infect Dis*. 1991;13(Suppl 2):S160-3.[39]

STUDY OVERVIEW		
Objectives	• To evaluate the efficacy of ceftriaxone to treat penicillin-susceptible streptococcal IE • To compare regimens of IV/IM ceftriaxone x4 weeks and IV/IM ceftriaxone x2 weeks followed by PO amoxicillin x2 weeks • To determine whether these regimens would be feasible for outpatient follow-up and/or treatment	
METHODS		
Overview	• Single center, randomized, open-label trial	
Inclusion/ exclusion criteria	• IE due to penicillin-susceptible streptococci, defined as bacteremia (≥2 set of positive blood cultures) plus one of the following: ○ New/changing regurgitant murmur ○ Predisposing heart disease ○ Vascular phenomena ○ Presence of vegetation on echocardiography	• Presence of CV risk factors (HF, severe aortic insufficiency, conduction system abnormalities) • Thromboembolic disease • Prosthetic valve IE (PVIE) • IE due to other organism besides penicillin-susceptible streptococci • Hypersensitivity to penicillins or cephalosporins
Interventions	• Patients randomized (1:1) to ceftriaxone 2 g IV/IM daily x4 weeks OR ceftriaxone IV/IM 2 g daily x2 weeks, then amoxicillin 1 g PO QID x2 weeks ○ Treated entirely as outpatients OR discharged and treated as outpatients once diagnosis made and risk factors ruled out • MIC measured for all streptococci • Obtained peak and trough ratios of serum bactericidal activity	
Outcomes	• **Primary outcome:** cure rate (no growth on cultures at follow-up) • **Secondary outcome:** treatment as outpatient, time to defervescence	
Statistical analysis	• Fisher's exact test: categorical variables	
RESULTS		
Enrollment	• N=30; 15 in comparator group, 15 in intervention group • Time to randomization from onset of symptoms: 38 days (range 4 to 115 days) • Demographics: age 61, female 33% • Cardiac involvement: aortic valve IE 50%, mitral valve IE 38%, both aortic and mitral valve IE 6% • Pathogen: VGS 50%, *S. bovis* 50% • Site of initial treatment: hospital 77%, home 23%	

	• PK/PD
	  ○ All patients: MIC_{90} of penicillin <0.12 mcg/mL, ceftriaxone <0.25 mcg/mL
	  ○ All patients: peak ratio of serum bactericidal activity ≥0.64 mcg/mL
	  ○ Trough ratio of serum bactericidal activity: >1:32 in 97% of patients, >1:2 in 3% of patients

Primary outcome	• 100% of patients in both treatment groups ○ Follow-up: 3 to 6 months

Secondary outcome	• 27 patients (90%) received treatment as outpatients
	  ○ 1 patient preferred hospitalization
	  ○ 2 patients developed complications in hospital after randomization (HF, CNS disorder)
	• Time to defervescence: comparator 1.1 days vs intervention 1.5 days

AUTHOR CONCLUSIONS	
Author's conclusions	• "Ceftriaxone, alone or followed by a course of amoxicillin, is an efficacious mode of treatment for infective endocarditis caused by penicillin-susceptible streptococci. Treatment with these agents can be administered predominantly on an outpatient basis."
CRITIQUE	
Study strengths	• MICs, serum peak and trough concentrations measured • Treatment and follow-up conducted primarily in outpatient setting • Reasonable MIC breakpoints • Echocardiography required for enrollment in study; however, type not specified (TTE vs TEE) • Choice of agents and dosing reasonable based on susceptibilities and PK/PD parameters
Study limitations	• Neither group allocation represented standard of care (in-hospital IV antibiotics x4 weeks) • Only patients with penicillin-susceptible streptococci studied • No description of how patients enrolled qualified for study; unable to determine how many would meet Modified Duke Criteria for Definite IE • Small sample size • No blinding • Broad exclusion criteria (e.g., HF, conduction system abnormalities) • No data provided regarding adherence • Variable time to follow-up (i.e., 3 to 6 months); primary endpoint of cure determined at follow-up • Minimal description of statistical tests used • Broad range of time from onset of symptoms to initiation of treatment (i.e., 4 to 115 days) • No safety outcomes measured • No description of screening process to determine patient eligibility or fraction of screened patients enrolled • Minimal description of patient characteristics at baseline • No details provided with respect to funding
Applicability	• First study to suggest efficacy of a stepdown to PO antibiotics and outpatient management of IE • Methodologic flaws significantly impact generalizability of results
Key takeaway	• Low-risk patients with IE due to penicillin susceptible streptococci may be successfully treated as outpatients with either IV/IM ceftriaxone x4 weeks or IV/IM ceftriaxone x2 weeks followed by PO amoxicillin x2 weeks • More robust studies are needed to confirm

Table 6. Heldman AW, Hartert TV, Ray SC, et al. Oral antibiotic treatment of right-sided staphylococcal endocarditis in injection drug users: prospective randomized comparison with parenteral therapy. *Am J Med.* 1996;101:68-76.[40]		
STUDY OVERVIEW		
Objective	• To compare the safety and efficacy of PO vs IV antibiotics in IVDUs with right-sided staphylococcal IE	
METHODS		
Overview	• Dual-center, randomized, open-label trial	
Inclusion/ exclusion criteria	• IVDU • Age ≥18 • Fever (>38°C [oral] or >38.3°C [rectal]) • Sustained staphylococcal bacteremia (≥2 sets of positive blood cultures w/o other identifiable source of infection)	• Clinical evidence of left-sided IE, meningitis, or osteomyelitis • Inability to tolerate PO medications • Prosthetic device • Sustained hypotension • Acute respiratory failure requiring mechanical ventilation • Required use of non-approved antibiotics during treatment or follow-up periods • Organism not sensitive to trial regimen • Elopement or discharge against medical advice

Interventions	• Patients presenting with a febrile illness consistent with right-sided IE randomized to PO or IV antibiotics
	  ○ PO: ciprofloxacin 750 mg BID + rifampin 300 mg BID x4 weeks
	  ○ IV: oxacillin 2 g IV Q4H OR vancomycin 1 g IV Q12H x4 weeks + gentamicin 2 mg/kg IV Q8H x5 days
	• Antibiotics dosing adjusted based on renal function
	• Study drugs discontinued in patients failing to meet all inclusion/exclusion criteria within 72 hours
	• Patients remained in hospital for the duration of antibiotic treatment plus an additional 7 days of observation
	• Blood cultures obtained on days 6, 7 post-treatment and whenever fever recurred
	• Duration: 1 month after completion of antibiotics and observation	

Outcomes	• **Primary outcome:** treatment cure (per blood culture drawn on inpatient days 6, 7 post-treatment) • **Secondary outcomes:** treatment cure (per blood culture drawn on outpatient day 35 post-treatment), composite of primary outcome and projected cure (to include patients lost to follow-up) • **Safety:** drug toxicity, hepatoxicity, nephrotoxicity	

Statistical analysis	• Aimed to enroll 84 patients to provide the trial with 90% power to detect a 20% difference in cure rates with two-sided alpha of 0.05
	• Fisher's exact test: categorical variables
	• Bayesian analysis: compensate for wide confidence intervals
	• Primary analysis: per protocol
	  ○ Patients that met any of the exclusion criteria following enrollment were not included in the primary efficacy analysis
	  ○ Patients had to complete treatment and follow-up	

	• Secondary analysis
	  ○ Treatment success: ≥14 days of antibiotics, afebrile ≥24 hours, did not return within 60 days for retreatment
	  ○ Treatment failure: change of therapy due to persistent fever or suspicion of treatment inadequacy

RESULTS	

Enrollment	• N=85; 40 in PO arm, 45 in IV arm
	  ○ Completed treatment and follow-up: n=44 (n=19, 25, respectively)
	• Demographics: age 35, women 45% (PO 52%, IV 37%), black 92%
	• Comorbidities: HIV 68%
	• Pathogen: MSSA 95%, MRSA 5%
	• Diagnosis: definite IE 18%, probable IE 30%, possible IE 52%
	• Reasons for attrition (see Table II for complete list)
	  ○ Failed to meet inclusion criteria 8.6%
	  ○ Met exclusion criteria after entry 13%
	  ○ Antibiotic violation 12%
	  ○ Discharged against medical advice 12%

Primary outcome (PO vs IV)	• 95% vs 88% (OR 0.4, 95% CI 0.01 to 5.5)
Secondary outcomes (PO vs IV)	• 68% percent of patients presented for outpatient follow-up at day 35 post-treatment ○ All had repeat negative blood cultures • Secondary analysis: cure rates similar between groups (90% vs 91%, OR 1.2, 95% CI 0.1 to 7.1)
Safety (PO vs IV)	• Drug toxicity lower in PO (2.8% vs 62%, p<0.0001) • Hepatotoxicity: 2.8% vs 33% (p=0.0007) • Nephrotoxicity: 0% vs 26% (p=0.001)
AUTHOR CONCLUSIONS	
Author's conclusions	• "For selected patients with right-sided staphylococcal endocarditis, oral ciprofloxacin plus rifampin is effective and is associated with less drug toxicity than is intravenous therapy."
CRITIQUE	
Study strengths	• Patients in the intervention group were initiated on, rather than transitioned to, PO antibiotics • Secondary analysis performed to predict effect of dropout and loss to follow-up • Early randomization to limit selection bias
Study limitations	• Only IVDUs with staphylococcal right-sided IE studied • Echocardiography not required for participation in trial; left-sided IE ruled out based on absence of common signs (e.g., aortic or mitral valve murmur) • Majority of patients enrolled had possible IE • High attrition rate (48%); similar between treatment arms • Small sample size • Patients completed antibiotics and observation in hospital • Primary efficacy analysis determined per protocol • Restrictive exclusion criteria (non-approved antibiotics, prosthetic devices) • Many patients lost to outpatient follow-up (32%) • No report on which valves affected

	• Unblinded study design without endpoint adjudication • Standardized, as opposed to weight-based, vancomycin dosing may have contributed to increased nephrotoxicity in IV arm
Applicability	• Limited generalizability as population studied not characteristic of typical IE patients • Relatively low rates of resistance to oxacillin (5%) and ciprofloxacin (2%) seen in study compared to current rates in the US and many parts of the world • Only RCT in which patients were started on, rather than transitioned to, PO antibiotics
Key Takeaway	• IVDUs with right-sided native valve IE may have similar cure rates with PO ciprofloxacin plus rifampin as compared to the standard of care if the regimen is completed in-hospital

Table 7. Demonchy E, Dellamonica P, Roger PM, Bernard E, Cua E, Pulcini C. Audit of antibiotic therapy used in 66 cases of endocarditis. *Med Mal Infect.* 2011;41(11):602-7.[41]		
STUDY OVERVIEW		
Objective	• To assess the quality of antibiotic therapy prescribed for IE in the infectious diseases ward at a teaching hospital in France	
METHODS		
Overview	• Single center, retrospective, case-control study	
Inclusion/ exclusion criteria	• Definite IE or possible IE (per modified Duke criteria) and/or positive culture from valve or intracardiac device sample • Hospital admission between 2007 and 2009	• None

Interventions	• Management of IE not based on diagnostic or therapeutic protocol
	• Regimens assessed for appropriateness of drug, dose, route, frequency, and duration based on 2004 ESC guideline recommendations
	  ○ Discrepancy in ≥1 criterion deemed "not appropriate"
	  ○ 20% variation in dose or duration accepted
	• Most common PO regimens: amoxicillin or fluoroquinolone ± rifampin, linezolid	

Statistical analysis	• Fisher's exact test: categorical variables	
RESULTS		
Enrollment	• N=66; 19 patients (29%) were transitioned from IV to PO antibiotics • Demographics: age 63, female 30% • Comorbidities: DM 22%, severe renal insufficiency 8%, cirrhosis 8% • Cardiac involvement: aortic valve IE 52%, mitral valve IE 23%, both aortic and mitral valve IE 3%, tricuspid valve IE 5%, CIED-IE 6%, both tricuspid valve and CIED-IE 8%, NVIE 59%, PVIE 24% • Pathogen: Streptococci 38%, MSSA 17%, MRSA 2%, CONS 14%, *E. faecalis* 3% • Diagnosis: definite IE 84%, possible IE 11%	

Outcomes	• First-line antibiotic therapy in compliance with recommendations: 14%
	• Most common causes of inappropriate prescribing:
	  ○ Gentamicin dosed daily instead of in divided doses: 55%
	  ○ Gentamicin duration too long in staphylococcal IE: 32%
	  ○ Rifampin use not recommended: 72%
	• Transition from IV to PO antibiotics: 19 patients (29%)	

	○ Average time to transition (mean, SD): 18 ± 9 days ○ Complications 79%, left-sided IE 63% ○ Streptococci 37%, MSSA 42%, MRSA 21% • Surgery: 42% • Overall mortality: 15% ○ Inappropriate vs appropriate antibiotic therapy: 14% vs 22% (p=0.62) ○ PO vs IV: 0% vs 21% (p=0.052) • Median follow-up: 90 days
AUTHOR CONCLUSIONS	
Author's conclusions	• "Infective endocarditis antibiotic treatment rarely complied with the 2004 European guidelines, but this did not have a negative impact on mortality. Switching antibiotic therapy from intravenous to oral route was common, even for complicated left-sided endocarditis, and was associated with a favorable outcome in all cases."
CRITIQUE	
Study strengths	• All patients treated for IE included in study regardless of prognosis or risk factors • In-hospital mortality (15%) comparable to that of other published studies
Study limitations	• Antibiotic regimens generally not in accordance with guideline recommendations (14%) • Retrospective, cohort study design cannot establish efficacy of transition to PO antibiotics • Patient characteristics among those receiving PO antibiotics not well delineated • Primary/secondary outcomes not specified • No mention of antibiotic dosing for PO regimens • Patients transitioned to PO antibiotics remained hospitalized throughout treatment duration • Aminoglycosides commonly used in study • Internal assessment of antibiotic appropriateness introduces potential bias
Applicability	• First case-control study to compare transition to PO vs IV only antibiotics
Key takeaway	• Patients with IE may be treated successfully with an antibiotic regimen that includes a transition from the IV to PO route • More robust studies are needed to confirm

Table 8. Mzabi A, Kernéis S, Richaud C, et al. Switch to oral antibiotics in the treatment of infective endocarditis is not associated with increased risk of mortality in non-severely ill patients. *Clin Microbiol Infect.* 2016;22(7):607-12.[42]		
STUDY OVERVIEW		
Objective	• Evaluate the safety and efficacy of a transition from IV to PO antibiotics in patients with IE	
METHODS		
Overview	• Single center, retrospective, case-control study	
Inclusion/ exclusion criteria	• Definite or possible IE (per Duke criteria) • Hospital admission between 2000 and 2012	• None
Interventions	• IV antibiotics administered as recommended per ESC guidelines • Patients could be transitioned from IV to PO antibiotics based on a local protocol if each of the following were met: minimum 7 days IV antibiotics, clinically stable, afebrile, CRP levels reduced, negative blood cultures, normal WBC and SCr, and improvement upon	

	imaging ○ Most popular regimens: amoxicillin; clindamycin + rifampin or fluoroquinolone; fluoroquinolone + rifampin (see Table 3 for complete list)
Statistical analysis	• Cox proportional hazards model: predictors of mortality • All clinically relevant variables tested via sequential univariate and multivariate analyses • Backward stepwise variable selection procedure applied to rule out variables that were not statistically significant
RESULTS	
Enrollment	• N=426; 214 were transitioned to PO antibiotics, 212 received IV antibiotics only • Demographics: age 65, women 32% • Comorbidities: DM 11% (PO 7%, IV 14%), CKD 11%, cirrhosis 4% (PO 2%, IV 6%) • Pathogen: Streptococcus 40%, *S. aureus* 19% (PO 13%, IV 25%, MRSA 3%), *E.* faecalis 12%, CONS 11% • Diagnosis: definite IE 87%, possible IE 13% • Cardiac involvement: left-sided IE 79%, right-sided IE 6%, PVIE 46%, CIED-IE 15% • Patient presentation: febrile 86%, acute HF 36% (PO 28%, IV 44%), healthcare-associated IE 25%, shock 11% (PO 4%, IV 17%) • Patients were transitioned to PO antibiotics after a median (range) 21 (0 to 70) days.
Outcomes	• Six independent risk factors for death identified: age >65, type 1 DM, immunosuppression, shock, disinsertion of prosthetic valve, and *S. aureus* ○ Transition to PO antibiotics not an independent risk factor for death • After adjusting for the six risk factors listed above, there were no significant differences in mortality, relapse, or reinfection (rates below listed as PO vs IV, respectively). ○ Mortality: 8% vs 36% ($p<0.001$) ○ Relapse: 0.9% vs 4% ○ Reinfection: 2% vs 4% • Follow-up conducted at a median (range) of 5 (0 to 147) months
AUTHOR CONCLUSIONS	
Author's conclusions	• "With a low relapse and reinfection rates, oral therapy is feasible in less severely ill patients with favorable outcome during the course of the treatment of IE. These results must be confirmed by prospective studies."
CRITIQUE	
Study strengths	• All patients with definite and possible IE during study period included regardless of prognosis or risk factors • Largest study assessing PO antibiotics in IE to date • Multivariate analysis allows for detection of confounding bias
Study limitations	• Retrospective, cohort study design does not allow for clear establishment of safety and efficacy of transition to PO antibiotics • Patients transitioned to PO antibiotics had fewer comorbidities, less-severe disease at onset, and less likely to be infected by *S. aureus* • Primary/secondary outcomes not specified • Highly variable time to transition to PO antibiotics in the intervention group • No mention of antibiotic dosing • Patients transitioned to PO antibiotics remained hospitalized throughout treatment duration • No report on which valves affected (only left- or right-sided IE)

Applicability	• Patients responded well to a transition to PO antibiotics, including many with high-risk conditions (e.g., prosthetic valves, CIEDs) • Patients that were transitioned to PO antibiotics tended to have less severe symptoms • Represents the largest observational study to date • Adds to a growing body of evidence suggesting that a transition to PO antibiotics may be appropriate in some patients
Key Takeaway	• In patients with IE and less severe symptoms, a transition to PO antibiotics after at least 7 days may have similar efficacy compared to continued IV antibiotics • Evidence from randomized controlled trials is needed to confirm

Table 9. Iversen K, Ihlemann N, Gill SU, et al. Partial oral versus intravenous antibiotic treatment of endocarditis. *N Engl J Med.* 2019;380(5):415-24.[43]

STUDY OVERVIEW		
Objective	• To compare the safety and efficacy of a transition from IV to PO antibiotics in stable patients with left-sided IE	
METHODS		
Overview	• Multicenter, randomized, open-label, non-inferiority trial	
Inclusion/ exclusion criteria	• Left-sided IE (per modified Duke criteria) • Infection with one of the following: Streptococci, *E. faecalis*, *S. aureus*, CONS • Age ≥18 • ≥10 days of appropriate IV antibiotics • ≥7 days s/p valve surgery • Afebrile ≥48 hours, CRP <25% peak, WBC <15 • No abscess formation or valve abnormalities requiring surgery	• BMI >40 • Concomitant infection requiring IV antibiotics • Immunosuppression • Suspicion of malabsorption • Poor compliance

Interventions	• Patients in stable condition randomized to transition from IV to PO antibiotics or continue IV antibiotics
	• PO antibiotic regimens developed by trial investigators; all consisted of two drugs with high PO bioavailability
	  ○ Regimens individualized for each patient based upon susceptibility results
	  ○ Most popular regimens: amoxicillin (AMX) + rifampin (RIF), AMX + moxifloxacin, dicloxacillin + RIF, AMX + linezolid (see Table S2 for complete list)
	  ○ Discharged patients seen 2 to 3 times per week until completion of antibiotic therapy	

Outcomes	• **Primary outcome:** composite of all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteremia with primary pathogen • **Secondary outcomes:** individual components of the primary composite outcome, median hospital LOS following randomization • **Safety:** plasma concentrations of PO antibiotics, adverse effects	
Statistical analysis	• Noninferiority margin: 10% • Aimed to enroll 400 patients to provide the study with 90% power to confirm noninferiority, based on estimated 10% event rate and 5% loss to follow-up • Student's t-test or Mann-Whitney U test: continuous variables • Chi-squared test: categorical variables	

<table>
<tr><td></td><td colspan="5">• Intention-to-treat (primary) and per-protocol analyses performed</td></tr>
<tr><td colspan="6">RESULTS</td></tr>
<tr><td>Enrollment</td><td colspan="5">• N=400; 201 in PO arm, 199 in IV arm
• Demographics: age 67, women 23%
• Comorbidities: DM 17%, CKD 12%, HD 7.0%, IVDU 1.2%
• Pathogen: Streptococcus 49%, E. faecalis 24%, S. aureus 22% (MRSA 0%), CONS 5.8%
• Cardiac involvement: mitral valve IE 34%, aortic valve IE 55%, PVIE 5.5%, CIED-IE 3.5%, valve surgery 38%
• Preexisting cardiac conditions: prosthetic valve 27%, pacemaker 8.8%, other valve disease 43%</td></tr>
<tr><td>Primary outcome (IV vs PO)</td><td colspan="5">• 12.1% vs 9.0% (OR 0.72, 95% CI 0.37 to 1.36); difference 3.1% (95% CI -3.4 to 9.6, p=0.40); criteria for noninferiority met
• All patients followed for 6 months after completion of antibiotic therapy; none lost to follow-up</td></tr>
<tr><td rowspan="6">Secondary outcomes (IV vs PO)</td><td>Component</td><td>IV</td><td>PO</td><td>Difference</td><td>HR (95% CI)</td></tr>
<tr><td>All-cause mortality</td><td>6.5%</td><td>3.5%</td><td>3.0 (-1.4 to 7.7)</td><td>0.53 (0.21 to 1.32)</td></tr>
<tr><td>Unplanned cardiac surgery</td><td>3.0%</td><td>3.0%</td><td>0 (-3.3 to 3.4)</td><td>0.99 (0.32 to 3.07)</td></tr>
<tr><td>Embolic event</td><td>1.5%</td><td>1.5%</td><td>0 (-2.4 to 2.4)</td><td>0.97 (0.20 to 4.82)</td></tr>
<tr><td>Relapse of bacteremia</td><td>2.5%</td><td>2.5%</td><td>0 (-3.1 to 3.1)</td><td>0.97 (0.28 to 3.33)</td></tr>
<tr><td colspan="5">• Median LOS in hospital after randomization was 19 days (IQR 14 to 35) vs 3 days (IQR 1 to 10) (p <0.001)
• 80% of patients in PO arm discharged prior to completion of antibiotic therapy
• No significant differences found in primary outcome within any subgroup analyzed</td></tr>
<tr><td>Safety/ compliance (IV vs PO)</td><td colspan="5">• Suboptimal plasma concentrations found in 3.5% of patients in PO arm
○ Primary outcome did not occur in any of these patients
• Adverse effects requiring change of therapy similar between groups (6.0% vs 5.0%, p=0.66)
• Similar findings between intention-to-treat and per protocol analyses</td></tr>
<tr><td colspan="6">AUTHOR CONCLUSIONS</td></tr>
<tr><td>Author's conclusions</td><td colspan="5">• "In patients who had endocarditis on the left side of the heart caused by streptococcus, E. faecalis, S. aureus, or coagulase-negative staphylococci and who were in stable condition, a shift from intravenously administered to orally administered antibiotic treatment was noninferior to continued intravenous antibiotic treatment."</td></tr>
<tr><td colspan="6">CRITIQUE</td></tr>
<tr><td>Study strengths</td><td colspan="5">• Assessed relevant, clinical outcomes
• Pathogens included are those that contribute most frequently to IE
• All patients enrolled had definite IE
• Study included patients with high-risk features (e.g., PVIE, CIED-IE)
• Baseline characteristics well-matched between study arms
• Limited crossover between groups
• No patients lost to follow-up
• Adjudication of clinical endpoints reduces cognitive bias</td></tr>
</table>

Study limitations	• Only patients with left-sided IE studied • No patients enrolled had MRSA IE • Only 20% of population screened was randomized • 30% of otherwise eligible patients excluded for not growing one of four studied pathogens • Patients were referred to the study by other physicians • No data provided regarding adherence in intervention group • IVDUs poorly represented (1.3%) • Morbidly obese patients (BMI >40) excluded
Applicability	• Patients that were transitioned to PO antibiotics responded well based on every measured outcome and across all subgroups • All patients were clinically stable at the time of randomization; most had NVIE • The three most common pathogens were streptococci, *E. faecalis*, and MSSA • Represents the largest, most well-designed RCT to date; contains the highest quality evidence to support a transition to PO antibiotics in stable IE
Key Takeaway	• In stable patients with left-sided IE due to Streptococcus, MSSA, *E. faecalis*, or CONS, it is reasonable to recommend a transition to PO antibiotics after at least 10 days, assuming PO tolerability and a proven history of medication adherence

Table 10. Tissot-Dupont H, Gouriet F, Oliver L, et al. High-dose trimethoprim-sulfamethoxazole and clindamycin for staphylococcus aureus endocarditis. *Int J Antimicrob Agents.* 2019;54(2):143-8.[44]		
STUDY OVERVIEW		
Objective	• To evaluate the safety and efficacy of IV TMP-SMX and clindamycin (T&C) +/- rifampin and gentamicin with a transition to PO T&C for the treatment of *S. aureus* IE	
METHODS		
Overview	• Single center, quasi-experimental, pre-post study (retrospective, case-control study)	
Inclusion/ exclusion criteria	• Definite IE (per Modified Duke Criteria) • Referral between 2001 and 2016	• None
Interventions	• Beginning 2001: [IV oxacillin 12 g/day (MSSA) OR IV vancomycin 30 mg/kg/day (MRSA)] x6 weeks + gentamicin 3 mg/kg x5 days • Beginning 2012: [IV TMP-SMX 160/800 mg Q4H + IV clindamycin 600 mg TID] x7 days, then PO TMP-SMX 960/4800 mg daily x5 weeks ○ IV rifampin 1800 mg/day and gentamicin 180 mg/day added if blood cultures remained positive after 48 h or if cardiac abscess present • All implicated pathogens susceptible to regimens • Doses of oxacillin, vancomycin, gentamicin, and TMP-SMX adjusted for renal function	
Outcomes	• **Primary outcome:** mortality • **Secondary outcomes:** hospital LOS, causes of death within 30 and 90 days • **Safety:** acute renal failure	
Statistical analysis	• Student's t-test: continuous variables • Fisher's exact test: categorical variables • Logit linear regression: multivariate analysis • Intention-to-treat (primary) and per-protocol analyses performed	

RESULTS	
Enrollment	• N=341; 171 in T&C group, 170 in control group • Demographics: age 62, women 30% • Comorbidities: HTN 30%, DM 20%, CKD 15%, HD 4.4%, IVDU 14%, HIV 2.7% • Pathogen: MSSA 88%, MRSA 12% • Cardiac involvement: aortic valve IE 33%, mitral valve IE 33%, tricuspid valve IE 20%, PVIE 23%, CIED-IE 27%, vegetation 73% (T&C 64%, control 82%) • Patient presentation: febrile 84% (T&C 78%, control 89%), acute HF 24%, rifampin/gentamicin 23% (T&C)
Primary outcome (T&C vs control)	• Global: 19.3% vs 30.0% (OR 0.56, 95% CI 0.35 to 0.92, p=0.024) ○ Median follow-up: 166 days • 30-day: 7.1% vs 14.2% (OR 0.46, 95% CI 0.22 to 0.96, p=0.05) • 90-day: 16.4% vs 21.2% (p=0.32) • In-hospital: 9.9% vs 18.2% (p=0.03) • 1-year: 19.8% vs 26.5% (p=0.16)
Secondary outcomes (T&C vs control)	• Hospital length of stay: 29.8 ± 3.8 days vs 39 ± 5.2 days (p=0.005) • 30-day mortality due to sepsis: 41.7% vs 41.7% (p=1) • 90-day mortality due to sepsis: 29.6% vs 40.0% (p=0.43) • Septic failure: 5.8% vs 8.2% (p=0.41) • Surgery: 52.1% vs 67.1% (p=0.006) • Relapses: 7.6% vs 12.9% (p=0.11)

Safety/ compliance (T&C vs control)	• Treatment discontinuation due to renal failure: 5.3% vs 0.6%
	• Renal dose adjustment required: 34% vs 10%
	• Compliance with protocol did not differ significantly between 2 groups
	  ○ Antibiotic modifications: 19% vs 26% (p=0.16)
	  ○ Microbiologic failure: 5.8% vs 5.9%
	• Per-protocol analysis
	  ○ No difference in global mortality (20.3% vs 29.4%, p=0.11)
	  ○ Septic failure more common in control group (2.2% vs 3.5%, p=0.02)

AUTHOR CONCLUSIONS	
Author's conclusions	• "The management of *S. aureus* IE, using a rapid switch to oral administration of T&C, reduced the hospital length of stay, mortality rate, and sepsis-induced multiple organ dysfunction syndrome. This treatment is a safe alternative for *S. aureus* IE."
CRITIQUE	
Study strengths	• All patients transitioned to PO step-down regimen beginning in 2012 regardless of prognosis or risk factors; excludes possibility of selection bias • Assessed relevant, clinical outcomes • All patients enrolled had definite IE • *S. aureus* IE is associated with a worse prognosis • Study included patients with high-risk features (e.g., PVIE, CIED-IE) • Multivariate analysis allows for detection and reduction of confounding bias • Comprehensive review of baseline characteristics • Provides information regarding compliance with antibiotic protocols • Reasonable antibiotic dosing based on ESC guidelines, although IV rifampin 1800 mg/day plus gentamicin 180 mg/day x7 days is without known precedent

Study limitations	• Patients not randomized • Patients in T&C group had fewer vegetations at baseline, suggestive of less severe disease • Only patients with *S. aureus* IE studied • Relatively low rates of MRSA (12%) • Use of IV rifampin/gentamicin common in the T&C group (23%) • Patients in T&C group remained in the hospital for an average of 29 days • Patients were referred to the study by other physicians • Renal dosing of antibiotics not provided
Applicability	• Does not carry same weight of evidence as a clinical trial, but provides several advantages over a traditional retrospective, case-control study • TMP-SMX for treatment of *S. aureus* IE recommended in ESC guidelines but not AHA/IDSA guidelines • Study demonstrated improved mortality in IE by converting to PO antibiotic-based regimen • Adds further evidence that transition to PO antibiotics is a valid alternative to standard of care
Key Takeaway	• In patients with *S. aureus* IE, 1 week of IV T&C followed by 5 weeks of PO T&C improved mortality and decreased hospital LOS as compared to 6 weeks of IV oxacillin or vancomycin.

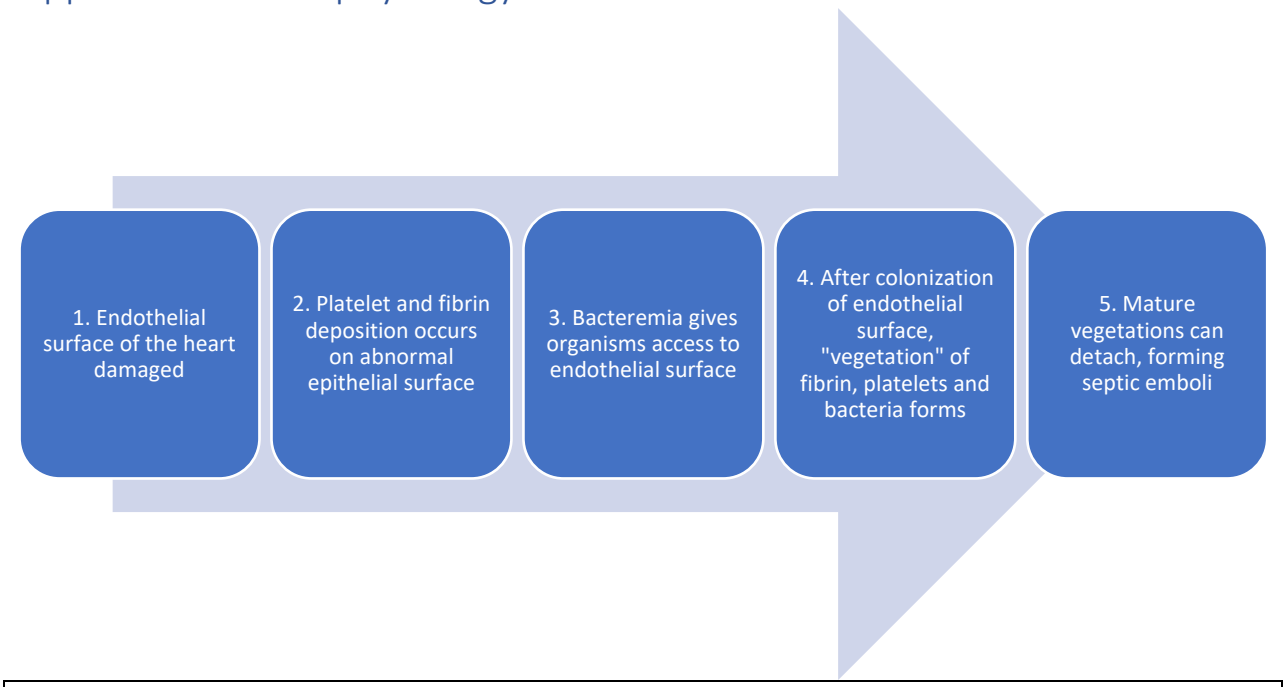
Summary and Recommendations

- Evidence from recent studies is challenging a long-held notion that IE must be treated with extended durations of IV, as opposed to PO, antibiotics.
- Recommendations to support a transition to PO antibiotics can now be made for NVIE caused by streptococci and methicillin-susceptible staphylococci (MSSA), as these clinical scenarios have been studied the most in clinical trials and high-quality observational studies.
- The following regimens can be used as PO stepdown therapy to treat susceptible pathogens, as appropriate:

Table 11. PO Stepdown Regimens for Treating IE Caused by Susceptible Pathogens	
Streptococci	MSSA
Amoxicillin 1 g QID ± rifampin 600 mg BID	Dicloxacillin 1 g QID + rifampin 600 mg BID
	TMP/SMX 480mg /2400 mg (3 DS tablets) BID

- To be considered for PO step-down therapy, patients should meet ALL the following criteria:
  - NVIE (left- or right-sided) caused by VGS or MSSA
  - Bacteremia cleared
  - Clinically stable (afebrile ≥48 hours, WBC <15)
  - ≥7-10 days of appropriate IV antibiotics
  - ≥7 days s/p valve surgery
  - No suspicion of malabsorption or poor compliance
  - No allergies to or significant drug interactions with any component of the regimen
  - Consent to telephone follow-up within 2 days and in-person follow-up within 2 weeks of hospital discharge

Appendix A: Pathophysiology of IE



[1] Endothelial lesions may result from various factors, including turbulent blood flow (as with rheumatic carditis) mechanical injury by catheters, or abrasion by solid particles (often due to IVDU). [2] Exposed subendothelial matrix triggers the deposition of fibrin-platelet clots, a process referred to as *nonbacterial thrombotic endocarditis*. [3] Bacteremia is the product of trauma to a mucosal surface with a high concentration of resident bacteria (e.g., oral cavity, GI tract), often during a dental procedure or a GI/GU surgery. Staphylococci, VGS, and enterococci are the pathogens most likely to adhere to the resulting complex. [4] Bacteria gain access to the endothelium and colonize the tissue, protected from host defenses (and antibiotics) within a layer of fibrin and platelets. The vegetation begins to grow. [5] Vegetations may be friable, such that fragments break off and travel downstream toward target organs. The resultant *septic emboli* are responsible for many of the characteristic signs, as well as complications, of IE.[45-46]

Appendix B: Patient Presentation

Table B1. Clinical Presentation of Infective Endocarditis[6,47,48]	
Symptoms	Fever, chills, weakness, dyspnea, cough, night sweats, weight loss, and/or malaise
Signs	Fever (common), heart murmur (common), CHF, cardiac conduction abnormalities, cerebral manifestations, embolic phenomenon, splenomegaly, skin manifestations (e.g., Osler's nodes, Janeway lesions)
Laboratory Tests	Continuous bacteremia (three sets of cultures/24 h); WBC normal or slightly elevated; possible anemia, thrombocytopenia, elevated ESR or CRP, and/or altered urinalysis (proteinuria/microscopic hematuria)
Other Diagnostic Tests	Echocardiogram (TTE/TEE), ECG, chest X-ray

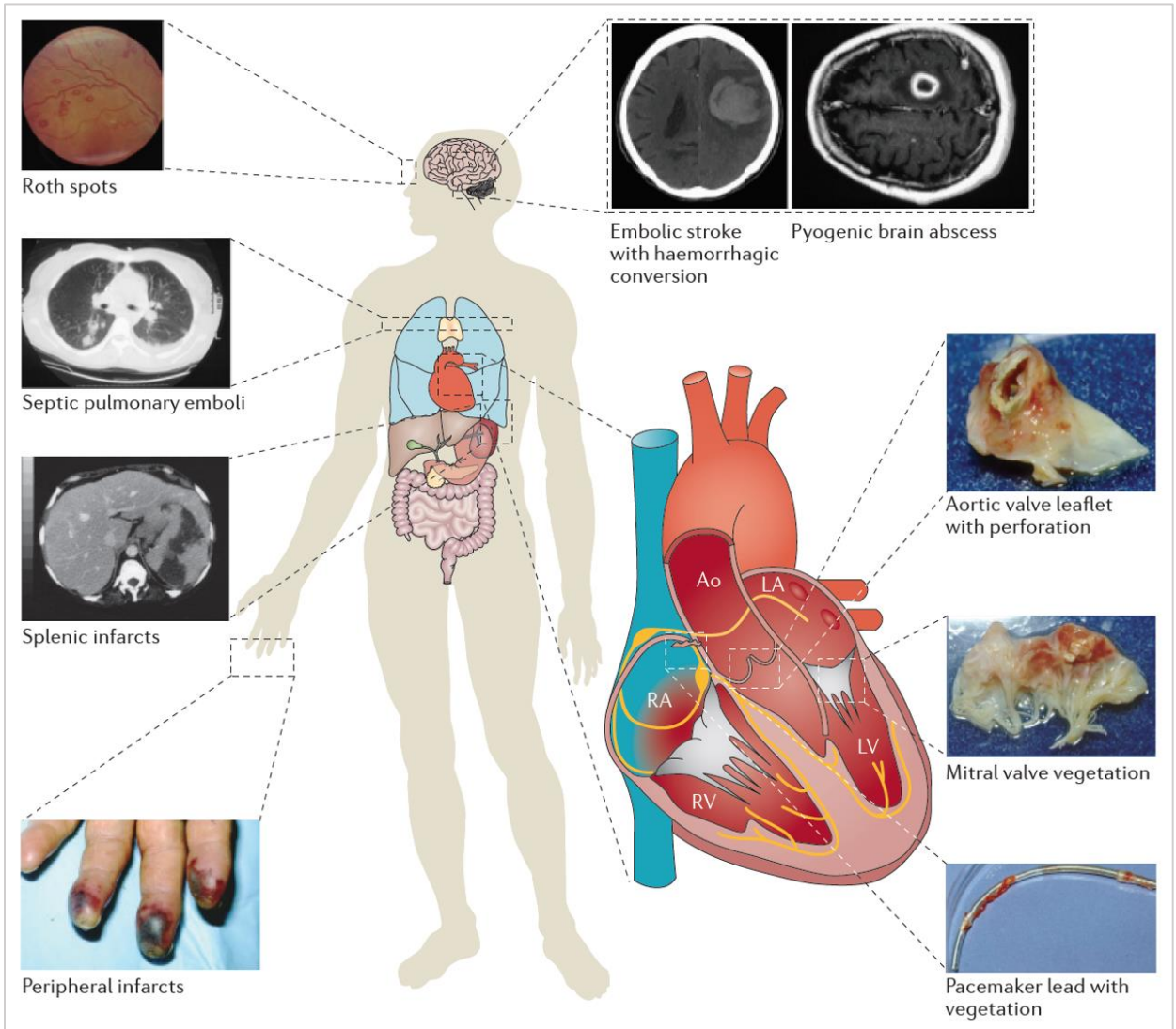


Figure B1. End-Organ Manifestations of IE[14]

Appendix C: Diagnosis

Table C1. Diagnosis of Infective Endocarditis Per the Modified Duke Criteria[45,46]	

Definite IE	• Pathological criteria
	  ○ Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis
	• Clinical criteria
	  ○ Two major criteria, or
	  ○ One major criterion and three minor criteria, or
	  ○ Five minor criteria

Possible IE	• One major criterion and one minor criterion, or • Three minor criteria
Rejected IE	• Firm alternative diagnosis explaining evidence of infective endocarditis, or • Resolution of infective endocarditis syndrome with antimicrobial therapy for four or fewer days, or • No pathological evidence of infective endocarditis at surgery or autopsy, with antimicrobial therapy for four or fewer days, or • Does not meet criteria for possible infective endocarditis, as above

Table C2. Duke Major Criteria[45,46]	

1. Blood culture positive for infective endocarditis	• Typical microorganisms consistent with IE from two separate blood cultures:
	  ○ VGS
	  ○ *Streptococcus bovis*
	  ○ HACEK group
	  ○ *Staphylococcus aureus*
	  ○ Community-acquired enterococci in the absence of a primary focus, or
	• Microorganisms consistent with IE from persistently positive blood cultures defined as follows:
	  ○ At least two positive blood cultures drawn greater than 12 hours apart, or
	  ○ Three or a majority of four or more separate cultures (with first and last sample drawn at least 1 hour apart)
	• Single positive blood culture for *Coxiella burnetii* or antiphase I immunoglobulin G antibody titer >1:800

2. Evidence of endocardial involvement	• Echocardiogram positive for infective endocarditis (transesophageal echocardiography recommended for patients with prosthetic valves, rated at least “possible infective endocarditis” by clinical criteria, or complicated infective endocarditis [paravalvular abscess]; transthoracic echocardiography as first test for other patients), defined as follows:
	  ○ Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets or on implanted material in the absence of an alternative anatomic explanation; or abscess; or
	  ○ New partial dehiscence of prosthetic valve
	  ○ New valvular regurgitation (worsening or changing of preexisting murmur not sufficient)

Table C3. Duke Minor Criteria[45,46]
1. Predisposition, predisposing heart condition, or injection drug use 2. Fever, temperature >38°C (100.4°F) 3. Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurism, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions 4. Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid fever 5. Microbiologic evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with infective endocarditis

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