https://doi.org/10.31925/farmacia.2026.4.2 **REVIEW**

INFECTIVE ENDOCARDITIS - CURRENT UNDERSTANDING OF PATHOGENIC MECHANISMS AND NEW MANAGEMENT OPTIONS

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Abstract

Infective endocarditis (IE) remains a significant global health challenge with increasing incidence and high mortality. The 2023 Duke-ISCVID criteria represent an important diagnostic update, incorporating advanced imaging modalities and microbiological criteria. Management continues to require a multidisciplinary approach with early involvement of infectious disease specialists and cardiac surgeons. The most significant update is the validation of oral step-down antibiotic therapy for selected patients with left-sided IE. The POET trial and further implementation studies have demonstrated that this approach is safe, effective, and associated with reduced hospital stays and potentially improved mortality in carefully selected minority of endocarditis patients. The ongoing dynamics of IE epidemiology and microbiology need permanent surveillance and periodic updates to diagnostic and therapeutic guidelines. This review summarizes current evidence on pathogenesis, clinical updates, microbiology, and the emerging role of oral antibiotic therapy. It also synthesizes data from major guidelines (American Heart Association, European Society of Cardiology, Duke-ISCVID criteria), trials (POET), and recent implementation studies.

Rezumat

Endocardita infecțioasă rămâne o provocare pentru sănătatea globală, cu o incidență în continua creștere și o mortalitate persistent ridicată. Criteriile Duke-ISCVID din 2023 reprezintă o actualizare majoră a metodelor de diagnostic, încorporând metode imagistice avansate și criterii microbiologice extinse. Managementul acestei patologii continuă să necesite o abordare multidisciplinară, cu implicarea timpurie a specialiștilor în boli infecțioase și a chirurgilor cardiaci. Cel mai semnificativ progres recent este validarea terapiei antibiotice orale pentru pacienți stabili cu endocardită infecțioasă (EI). Studiul POET și studiile ulterioare de implementare au demonstrat că această abordare este sigură, eficientă și asociată cu o reducere a spitalizării și o potențială îmbunătățire a ratei mortalității într-o minoritate atent selectată de pacienți cu EI. Evoluția continuă a epidemiologiei și microbiologiei EI necesită supraveghere continuă și actualizări periodice ale ghidurilor diagnostice și terapeutice. Acest studiu integrează dovezile actuale privind patogeneza, actualizările clinice, microbiologia și rolul terapiei antibiotice orale. De asemenea, sintetizează date din ghidurile importante (*American Heart Association, European Society of Cardiology*, criteriile Duke-ISCVID), studii clinice de referință (POET) și studii recente de implementare.

Keywords: infective endocarditis, oral therapy, POET study, Duke criteria

Introduction

Infective endocarditis (IE) remains a life-threatening infection with significant morbidity and mortality even if advances in diagnosis and treatment have been made. Globally, both the number of cases and the number of associated deaths have increased over the last three decades, from 478,000 cases in 1990 to over 1,090,000 in 2019, with number of deaths increasing from 28,750 to 66,320 during the same period (1, 2). The annual incidence has gradually increased over multiple years/decades, reaching 13.8 *per* 100,000 persons at present (1, 3). Men seem to have a higher incidence compared with women, ranging from 3:2 to 9:1; however, mortality-to-incidence ratios are higher in women, suggesting worse outcomes in female patients (1).

The epidemiological profile of IE is changing constantly. In developing countries, rheumatic heart disease remains the most common predisposing condition, while in more developed countries, degenerative valvular diseases, congenital abnormalities, and intracardiac devices seem to be more frequent (4, 5). The emergence of healthcare-associated infections, increasing intravenous drug use (6, 7), and the aging population have contributed to these changes (8). Socioeconomic differences also influence outcomes, patients from low- and middle-income countries exhibit more frequent complications and higher mortality rates

(23.7% *vs*. 15.0%) compared with those from more developed countries (1).

This review summarizes the current understanding of pathogenic mechanisms in both native and prosthetic valve endocarditis, updates on clinical presentation and microbiology, and emerging management strategies including the shift toward oral antibiotic therapy.

Method and Literature Selection

This narrative review was developed through targeted literature searches performed between January and March 2026 and focused primarily on publications available in PubMed/MEDLINE, using the following keywords: infective endocarditis, oral antibiotic therapy, POET, prosthetic valve endocarditis, Duke criteria, infective endocarditis pharmacotherapy. Priority was given to international guidelines, landmark clinical trials, recent review articles, and selected observational studies published predominantly between 2018 and 2026. Articles published in English were preferentially selected. Given the narrative design of the manuscript a formal systematic screening process was not performed; literature selection aimed to provide a thematic synthesis of contemporary evidence rather than a systematic analysis and we selected the studies based on their scientific relevance, impact on clinical practice, citation frequency, and contributions to key developments in the field. The final selection aimed to provide a balanced overview of contemporary evidence regarding clinical updates and microbiology, native valve and prosthetic valve endocarditis pathogenesis and antibiotic therapy use.

Clinical Updates and Microbiology

Infective endocarditis (IE) epidemiology has changed significantly in the past decades, studies showing a shift from a disease historically linked to rheumatic heart disease and poor dental health to one dominated by healthcare-associated and iatrogenic exposure (9). The risks nowadays consist of advanced age or the use of cardiovascular procedures (invasive or minimally invasive) such as prosthetic valves, transcatheter implants, implantable cardiac devices. Nowadays patients with IE are older, have more comorbidities, and are more exposed to healthcare-associated infections. In other areas, such as North America and parts of Western Europe, IE rates have increased in younger populations because of intravenous drug use (IDU) (10).

In 2023 the *Duke-International Society for Cardiovascular Infectious Diseases* (ISCVID) criteria had been updated to incorporate new diagnostic capabilities: molecular diagnostic methods (polymerase chain reaction (PCR), metagenomic sequencing, in situ hybridization), advanced imaging (PET-CT and cardiac CT as major criteria equivalents). Also, the involved pathogens list was extended and the risk factor include transcatheter valves and cardiac device leads (11). The European Society of Cardiology established similar guidelines in 2023, emphasizing the importance of multidisciplinary involvement, constituted in "endocarditis teams" (12).

Recent literature underlines the importance of early surgery (ideally within 7 days for complicated cases), which has been associated with improved outcomes and fewer embolic events. On the other hand, for stable cases, outpatient parenteral antibiotic therapy (OPAT) and step-down oral regimes have shown good results (13).

Traditionally, IE has been linked to Gram-positive organisms, especially *Staphylococcus aures*, *viridans group Streptococci*, and *Enterococci*. Recent data confirm this pattern (14), but new discoveries have been made. The updated 2023 Duke-ISCVID criteria expanded the pathogens list: almost all *Streptococcal* species (with the exception of *Streptococcus pneumoniae* and *Streptococcus pyogenes*) are now considered typical IE causative agents, along with *Staphylococcus lungdunensis*, *Granulicatella* and *Abiotrophia* species, and various organisms in the context of intracardiac prostheses (15).

S. aureus has replaced streptococci as the worldwide leading causative pathogen for IE even in low- and middle-income countries (16). Even if Gram-negative bacteria are less commonly implicated in the aetiology of IE, they pose major therapeutic challenges. IE caused by *Pseudomonas aeruginosa* was historically classified as community-acquired, being associated with IDU in 90% of cases. However, given the shift towards healthcare-associated IE, the literature describes cases of *P. aeruginosa* IE in patients with history of intravascular device-related procedures, cardiac catheterization, pacemaker insertion, open heart surgery and even transcatheter aortic valve implantation (TAVI). Excessive alcohol consumption, in patients with or without cirrhosis, was recorded as a potential risk factor for *Escherichia coli* IE probably due to bacterial translocation from the damaged gastrointestinal tract mucosa (15).

Culture-negative IE still poses a challenge, requiring taking into consideration prior antibiotic exposure and intracellular pathogens (17). Advanced molecular diagnostic techniques, especially metagenomic next-generation sequencing (mNGS), can detect rare or pathogens hard to grow in culture in resected valve tissue with sensitivity of approximately 80% and good specificity.

Despite multiple advantages, molecular techniques have higher costs, reduced availability and pose a challenge in distinguishing contamination from true infection. Also, they do not specify the antimicrobial susceptibility profile, meaning that culture is still necessary as a susceptibility-detecting method (18).

Native Valve IE Pathogenesis

The pathogenesis of native valve IE involves a sequence of events beginning with endothelial injury and culminating in vegetation formation. Normal valvular endothelium is naturally resistant to bacterial colonization; thus, infection typically requires prior endothelial damage.

The initiating event is an injury to the valvular endothelium or endocardium, which exposes subendothelial collagen and other matrix molecules. Platelets and fibrin adhere to these exposed surfaces, forming a micro thrombotic lesion representing nonbacterial thrombotic endocarditis (NBTE) (19). This sterile vegetation serves as a site for subsequent bacterial colonization during transient bacteraemia (20).

Bacteria circulating in the bloodstream bind to and colonize NBTE lesions through specialized surface adhesins. Gram-positive cocci, the predominant pathogens, express multiple adhesins that serve as virulence factors by enhancing attachment to host cell substrates and extracellular matrix proteins. These adhesins mediate attachment to fibronectin, fibrinogen, and other matrix molecules, facilitating both initiation and propagation of infection (21, 22).

Once established, bacteria replicate in situ, stimulating further platelet and fibrin deposition to form an infected vegetation. Vegetations create a protective microenvironment poorly accessible to neutrophils and host defence molecules (5). Bacterial densities within vegetations reach extremely high levels (10^9 to 10^{10} colony-forming units per gram), promoting high-grade bacteraemia and further vegetation growth (23).

The inflammatory cascade involves multiple cytokines associated with integrins, tissue factors, and adhesion molecules, which attract monocytes and platelets with associated fibronectin production, leading to thrombus formation. This creates a cycle that further activates inflammation against host defences (1).

Biofilm formation represents another critical virulence mechanism. Many IE-associated microorganisms produce biofilms that allow bacterial populations to embed within an extracellular polysaccharide matrix with quorum sensing and synchronized gene expression. Once established, biofilms protect bacteria from host immune defences, impede antimicrobial efficacy, and harbour resistant persistent organisms (24).

Four mechanisms drive most clinical features and complications: (i) valvular destruction, paravalvular extension, and heart failure; (ii) microvascular and large-vessel embolization; (iii) metastatic infection of target organs; and (iv) immunologic phenomena such as hypocomplementemia glomerulonephritis (5).

Newer studies have shown new pathogenesis mechanisms, such as the formation of neutrophil extracellular traps (NET) or new molecular targets. Elevated IL-8 and the interaction between activated platelets and neutrophils trigger the formation of NETs. Many bacteria exhibit virulence mechanisms to survive NET formation. It was shown in studies that NETs physically interconnect and entrap bacteria-platelet aggregates inside vegetations, redefining them as structural architects of vegetation growth (25).

Another new studied mechanism is proteomic analysis that has identified key proteins including peptidoglycan recognition protein 1 (PGLYRP1), fibrinogen alpha chain (FGA), and superoxide dismutase 2 (SOD2) as playing roles in disease progression and as potential early diagnostic or therapeutic targets (26).

Prosthetic Valve IE Pathogenic Mechanisms and Management Implications

Prosthetic valve endocarditis (PVE) accounts for 20 - 30% of all IE cases. The incidence rate is 0.3 - 1.2 *per* 100 person-years, with a rapid increase in recent years. PVE is slightly more common with biological than mechanical prostheses (2.2% *vs*. 1.5% over 12 years) (1).

PVE pathogenesis has similar mechanisms as native valve IE, but includes additional factors related to prosthetic material. Biofilm formation is important in prosthetic valve infection, similar to other device-related infections. A biofilm creates an environment where antimicrobial agents and immune cells have difficulty penetrating, and metabolic changes in infecting organisms reduce antimicrobial efficacy. This explains the increased risk of infection relapse at prosthetic valve sites (23).

The microbiology of PVE is different in early (≤ 12 months post-surgery) from late (> 12 months) infections. Early PVE is associated with perioperative infections and the most common pathogens include *S. aureus*, coagulase-negative staphylococci (mostly methicillin-resistant), gram-negative rods, and fungi. *Mycobacterium chimaera* found in cardiopulmonary bypass heat-exchange systems has emerged as an important pathogen for early PVE and it represents a diagnostic challenge due to the indolent onset and high mortality risk. Late PVE has similar patterns with native valve IE, with viridans group streptococci being the most frequent pathogens (27).

IE following transcatheter aortic valve implantation (TAVI) shows a distinct microbiological profile. Enterococci are the leading cause, accounting for more than one-fourth of cases, likely explained by the widespread use of the transfemoral approach and enterococci's affinity for the inguinal region. *S. aureus* in TAVR-IE demonstrates high virulence, which results in doubling the hospital visits (47.8% *vs*. 26.9%) and increase in the 2-year mortality rate (71.5% *vs*. 49.6%) compared to other pathogens (24).

Management implications for PVE include more aggressive surgical intervention (27, 28). Current guidelines recommend early surgery for: (i) Heart failure due to valve dehiscence, intracardiac fistula, or severe prosthetic dysfunction (Class I recommendation); (ii) Persistent bacteraemia despite appropriate antibiotics for 5 - 7 days (Class I recommendation); (iii) IE complicated by heart block, annular or aortic abscess, or destructive penetrating lesions (Class I recommendation); (iv) PVE caused by fungi or highly resistant organisms (Class I recommendation); (v) Recurrent emboli despite appropriate antibiotic treatment (Class IIa recommendation); and (vi) Relapsing PVE (Class IIa recommendation).

A randomized controlled trial from South Korea showed that early surgery in asymptomatic patients with severe valve dysfunction and large vegetations (≥ 10 mm) significantly reduced embolic events (0% *vs*. 21%, p = 0.005) compared to conventional medical treatment (1).

Newer studies involving pathogenesis mechanisms have shown that biofilms on prosthetic valves are bacterial aggregates composed of self-produced extracellular polymeric substances (EPS), which is difficult to treat in cardiovascular infections. Current research is exploring strategies for degrading EPS, nanodrug delivery systems, and gene editing technology targeting drug resistance genes. EPS degradation represents an entirely new therapeutic frontier specific to prosthetic material infections (29).

General Update of Antibiotic Therapy Use

Empiric intravenous antibiotic therapy should be initiated promptly after obtaining blood cultures. The choice of antibiotics depends on epidemiological factors, local microbial sensitivity patterns, underlying cardiac disease, presence of infected implants, and immunological status.

For native valve IE, beta-lactam antibiotics remain preferred for susceptible strains (1). A study conducted in a multidisciplinary hospital in Bucharest, Romania analysed the multiple antibiotic resistance index (MARI) for *Streptococcus* spp. strains isolated between 2021 and 2024 from blood, urine, bronchial and tracheal secretions, sputum, wound secretions, CSF, ascites fluid, pleural fluid, joint fluid and intraoperatively collected secretions. The study showed that the MARI index for *Streptococcus* spp. recovered from blood cultures was close to 0.00 in 2021 and 2022, following a slight increase in 2023 (~ 0.02), then returning to 0.00 in 2024. The very low MARI values observed for *Streptococcus* spp. may indicate a good susceptibility profile and suggest a low prevalence of hospital-acquired resistance mechanisms. This profile may support the use of standard therapy in streptococcal infections, without the need for broader-spectrum therapeutic alternatives (30).

Cefazolin or vancomycin are alternatives for penicillin-allergic patients or methicillin-resistant *S. aureus* (MRSA). Daptomycin and linezolid can be used when vancomycin is ineffective or cannot be used (1).

A significant update is the down step of adjunctive aminoglycoside therapy for native valve endocarditis due to lack of mortality benefit and increased nephrotoxicity risk (31). For prosthetic valve endocarditis caused by staphylococci, combination therapy with rifampin and a short course of gentamicin remains recommended.

The optimal duration of antibiotic therapy is generally 4 weeks for most native valve cases and 6 weeks for prosthetic valve endocarditis. Treatment can be divided into two phases: an early critical phase comprising surgical or other interventions whilst receiving intravenous antibiotics (lasting until the patient becomes afebrile, with sterile blood cultures), followed by a continuation phase (1).

Long-acting lipoglycopeptide antibiotics (dalbavancin and oritavancin) pose an interest for IE treatment. Although not FDA-approved for IE and still lacking clinical trial data, these agents have been used with some success in selected cases. Their weekly or longer dosing intervals and the elimination of frequently intravenous catheter placement could improve prolonged therapy compliance (24).

Table I

Treatment options based on pathogen (13, 31-33)

Pathogen	Standard Therapy	Therapeutic Alternatives	Duration	Pharmacological Observations
1. Oral Streptococci & *S. gallolyticus* — Penicillin-Susceptible (Standard Dosing) [Class I-B]				
Viridans group Streptococci, S. gallolyticus Penicillin MIC ≤ 0.125 mg/L	**Penicillin G** 12 - 18 MU/day IV in 4 - 6 doses or continuous **Amoxicillin** 12 g/day IV in 4 - 6 doses **Ceftriaxone** 2 g/day IV once daily **2-week option (NVE only):** Penicillin G or Ceftriaxone + Gentamicin 3 mg/kg/day (normal renal fn)	**Vancomycin** (beta-lactam allergy) 30 mg/kg/day IV in 2 doses (4 wk NVE/6 wk PVE) Teicoplanin: loading 6 mg/kg/12 h x 3 days then 6 - 10 mg/kg/day (limited data)	**4 wk** NVE **6 wk** PVE **2 wk** short-course NVE	Cure rate > 95%. Ceftriaxone preferred for OPAT (once-daily). Short-course (2 wk) NOT applicable to PVE. Clindamycin NOT recommended for prophylaxis. Desensitisation is recommended if penicillin allergy confirmed. Class I-B (4/6-wk) | Class I-B (2-wk) | Class I-C (vancomycin)

Pathogen	Standard Therapy	Therapeutic Alternatives	Duration	Pharmacological Observations
2. Oral Streptococci & *S. gallolyticus* — Increased Exposure or Penicillin-Resistant [Class I-B]				
Viridans Streptococci, S. gallolyticus MIC 0.125 - 2 mg/L or resistant (> 2 mg/L)	**Penicillin G / Amoxicillin / Ceftriaxone** Same doses as section 1 + **Gentamicin** 3 mg/kg/day IV or IM × 2 weeks	**Vancomycin** (allergy) 30 mg/kg/day IV in 2 doses ± Gentamicin 2 wk (PVE only)	**4 wk** NVE **6 wk** PVE	Aminoglycoside mandatory ≥ 2 wk in resistant cases. Short-course (2 wk) regimen NOT recommended. Incidence of penicillin-resistant *S. mitis*/ *S. oralis* > 30% in large collections. Daptomycin experience is very limited. Class I-B
3. *Staphylococcus aureus* & CoNS — Methicillin-Susceptible (MSSA/MSCNS) [Class I-B]				
S. aureus (MSSA), S. lugdunensis, MSCNS	**(Flu)cloxacillin** 12 g/day IV in 4 - 6 doses **Cefazolin** 6 g/day IV in 3 doses **PVE adds:** Rifampin 900 mg/day IV/PO in 3 doses (start after 3 - 5 days, once bacteraemia cleared) + Gentamicin 3 mg/kg/day × 2 wk	**Cefazolin** (non-anaphylactic penicillin allergy) 6 g/day IV in 3 doses ± rifampin + gentamicin (PVE) **Daptomycin 10 mg/kg/day** + ceftaroline or fosfomycin (severe allergy) [Class IIb-C]	**4 - 6 wk** NVE **≥ 6 wk** PVE	Aminoglycosides NOT recommended in staphylococcal NVE (no benefit, increased nephrotoxicity). Cefazolin replaces cloxacillin only for non-immediate hypersensitivity. Rifampin ONLY in foreign-body IE (PVE), after bacteraemia cleared. *S. lugdunensis*: usually methicillin-susceptible. Class I-B
4. *Staphylococcus aureus* & CoNS — Methicillin-Resistant (MRSA/MRCNS) [Class I-B]				
MRSA, MRCNS	**Vancomycin** 30 - 60 mg/kg/day IV in 2 - 3 doses **PVE adds:** + Rifampin 900 - 1200 mg/day + Gentamicin 3 mg/kg/day × 2 wk	**Daptomycin 10 mg/kg/day** + cloxacillin, ceftaroline, or fosfomycin [Class IIb-C] Others: fosfomycin + imipenem; ceftaroline; quinupristin-dalfopristin; TMP-SMX + clindamycin (high dose)	**4 - 6 wk** NVE **≥ 6 wk** PVE	Target vancomycin AUC/MIC 400–600 mg·h/L (MIC assumed 1 mg/L). If MIC > 1 mg/L: switch therapy (nephrotoxicity risk). Daptomycin MUST be given at high dose (10 mg/kg) + combined agent. Hetero-VRSA prevalence 19 - 34%. PVE mortality > 45%; early surgery frequently required. Class I-B
5. *Enterococcus spp.* — Various Resistance Profiles				
E. faecalis (non-HLAR) Gentamicin MIC ≤ 128 mg/L	**Ampicillin/Amoxicillin** 12 g/day IV in 4 - 6 doses + **Ceftriaxone** 4 g/day IV in 2 doses (preferred) OR + Gentamicin 3 mg/kg/day × 2 wk	Teicoplanin, linezolid, daptomycin (limited data)	**6 wk** NVE **6 wk** PVE/ complicated NVE	Ampicillin + ceftriaxone equally effective as amp + gentamicin; preferred when HLAR. Double beta-lactam NOT active against *E. faecium*. Gentamicin shortened to 2 wk in non-HLAR *E. faecalis* (reduced nephrotoxicity). *E. faecalis* now classified as major microbiological criterion. Class I-B
E. faecalis HLAR Gentamicin MIC > 128 mg/L	**Ampicillin + Ceftriaxone** 12 g/day + 4 g/day IV for 6 wk	Aminoglycosides CONTRAINDICATED (no synergism). If streptomycin-susceptible: streptomycin 15 mg/kg/day in 2 doses may substitute.	**6 wk**	Gentamicin resistance in up to 75% of *E. faecalis* and *E. faecium* isolates. Ampicillin + ceftriaxone is the standard in HLAR regardless of streptomycin susceptibility. Class I-B
Beta-lactam resistant E. faecium	**Vancomycin** 30 mg/kg/day IV in 2 doses + **Gentamicin** 3 mg/kg/day × 2 wk	Quinupristin-dalfopristin (not *E. faecalis*), linezolid ≥ 8 wk (monitor haematology)	**6 wk**	Beta-lactam resistance via PBP5 alteration → use vancomycin-based regimens. If beta-lactamase producer: replace ampicillin with ampicillin-sulbactam. Class I-C
VRE (Vancomycin-Resistant Enterococcus)	**Daptomycin 10 - 12 mg/kg/day IV** + Ampicillin 12 g/day IV OR + Ertapenem 2 g/day IV OR + Ceftaroline 1800 mg/day IV OR + Fosfomycin 12 g/day IV	Linezolid 2 × 600 mg/day ≥ 8 wk; quinupristin-dalfopristin ≥ 8 wk (not *E. faecalis*)	**6 wk**	Combination MANDATORY to prevent daptomycin resistance. Fosfomycin carries high sodium load — risk of acute HF. Daptomycin is associated with eosinophilic syndromes (up to 15%). Consult ID specialist. Class I-C

Pathogen	Standard Therapy	Therapeutic Alternatives	Duration	Pharmacological Observations
6. HACEK Group (*Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*) [Class I-B]				
HACEK spp.	**Ceftriaxone** 2 g/day IV once daily	**Ampicillin 12 g/day IV** (if no beta-lactamase) + Gentamicin × 2 wk **Ciprofloxacin** 400 mg/8 - 12 h IV or 750 mg/12 h PO (less validated)	**4 wk** NVE **6 wk** PVE	Some HACEK produces beta-lactamases — ampicillin no longer first-line. Slow growth makes standard MIC tests difficult. Susceptible to 3rd-generation cephalosporins and fluoroquinolones. Class I-B
7. Non-HACEK Gram-Negative Bacteria (*Pseudomonas, Enterobacterales*, etc.)				
Non-HACEK GNB ~ 1.8% of IE cases (ICE cohort)	**Beta-lactam + Aminoglycoside** (bactericidal combination — prolonged therapy)	± Quinolones or cotrimoxazole. *In vitro* bactericidal testing recommended. Early surgery strongly favoured.	**6 wk**	Rare and severe — Endocarditis Team discussion mandatory. Monitoring of serum antibiotic concentrations is helpful. Combined surgical + medical treatment recommended in most cases. No specific class (expert consensus)
8. Blood Culture-Negative IE (BCNIE) **- Selected Pathogens**				
Coxiella burnetii (Q fever)	**Doxycycline 200 mg/day PO + Hydroxychloroquine 200 - 600 mg/day PO**	Doxycycline alone inferior (hydroxychloroquine alkalinises vacuoles, enhancing doxycycline activity)	**> 18 months**	Treatment success = anti-phase I IgG < 1:400, IgA and IgM < 1:50. Monitor hydroxychloroquine serum levels. IgG phase I > 1:800 = major diagnostic criterion. No specific class (expert consensus)
Bartonella spp.	**Doxycycline 100 mg/12 h PO × 4 wk + Gentamicin 3 mg/kg/day IV × 2 wk**	Ampicillin or ceftriaxone + aminoglycoside (alternative regimens reported)	**4 wk** doxy **2 wk** gentamicin	Treatment success expected in ≥ 90%. Serology IgG > 1:800 supports diagnosis. PCR from blood and vegetations. No specific class (expert consensus)
Brucella spp.	**Doxycycline 200 mg/24 h PO + Cotrimoxazole 960 mg/12 h PO + Rifampin 300 - 600 mg/24 h PO**	Gentamicin optional for first 3 weeks	**≥ 3 - 6 months**	Treatment success = antibody titre < 1:60. Consult ID specialist. No specific class (expert consensus)
Tropheryma whipplei (Whipple's disease)	**Doxycycline 200 mg/24 h PO + Hydroxychloroquine 200 - 600 mg/24 h PO**	Ceftriaxone 2 g/24 h IV × 2 - 4 wk then cotrimoxazole 800 mg/12 h PO. If CNS involvement: + sulfadiazine 1.5 g/6 h PO. Note: trimethoprim NOT active *vs*. T. whipplei.	**≥ 18 months**	Treatment remains highly empirical. Relapses are not infrequent. 16S rRNA tissue sequencing aids diagnosis. Consult ID specialist. No specific class (expert consensus)
9. Fungal Endocarditis				
Candida spp.	**Echinocandin (high dose)** OR **Liposomal amphotericin B** ± flucytosine Followed by long-term oral fluconazole suppression	Lifelong suppressive oral fluconazole after initial IV treatment. Low threshold for surgery.	**Prolonged IV** + lifelong oral suppression	Mortality > 50%. Mainly PVE, PWID, immunocompromised. Antifungal + surgery (low threshold). Consult Endocarditis Team + ID specialist. No specific class (expert consensus)
Aspergillus spp.	**Voriconazole** (drug of choice)	+ Echinocandin or amphotericin B (some experts). Suppressive azole therapy lifelong.	**Lifelong** oral suppression	Blood culture-negative. Leading cause of fungal BCNIE. Very high mortality. Surgery almost always necessary. Consult ID specialist. No specific class (expert consensus)
10. Empirical Therapy (Before Pathogen Identification)				
Community-acquired NVE	**Ampicillin 12 g/day IV + Ceftriaxone 4 g/day IV**	**Beta-lactam allergy:**	**Until**	Must cover staphylococci, streptococci, enterococci. Switch to

Pathogen	Standard Therapy	Therapeutic Alternatives	Duration	Pharmacological Observations
or Late PVE (≥ 12 months post-surgery)	OR + (flu)cloxacillin + gentamicin	Cefazolin OR Vancomycin + gentamicin [Class IIb-C]	pathogen identified (then switch) Then full targeted course	targeted therapy within 24 - 48 h. Cloxacillin/cefazolin superior to vancomycin for MSSA empirically. Class IIa-C
Early PVE (< 12 months) or Nosocomial/ Healthcare-associated IE	**Vancomycin 30 mg/kg/day IV** OR Daptomycin 10 mg/kg/day IV **+ Gentamicin 3 mg/kg/day + Rifampin 900 - 1200 mg/day**	Must cover MRSA, enterococci, non-HACEK GNB	**Until** pathogen identified	Rifampin covers biofilm-forming organisms on prosthetic material. CoNS should be covered in PVE. De-escalate immediately once organism identified. Class IIb-C

CoNS = coagulase-negative staphylococci; GNB = Gram-negative bacilli; HACEK = *Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella, Kingella*; HLAR = high-level aminoglycoside resistance; IE = infective endocarditis; IV = intravenous; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S. aureus*; MSSA = methicillin-susceptible *S. aureus*; NVE = native valve endocarditis; OPAT = outpatient parenteral antibiotic therapy; PO = per os; PVE = prosthetic valve endocarditis; PWID = people who inject drugs; TMP-SMX = trimethoprim-sulfamethoxazole; VRE = vancomycin-resistant *Enterococcus*

Pharmacology of Antibiotics in Infective Endocarditis

Endocardial vegetations consist of dense fibrin-platelet matrices that can include an extremely high bacterial load, creating a physical barrier that make antibiotic penetration very difficult. This aspect can predispose to relapse when drug concentrations fall below therapeutic thresholds. This pathological architecture explains the rationale for prolonged intravenous therapy, which aims to sustain bactericidal concentrations at the infection site over time.

The selection of antibiotics in IE is guided by distinct pharmacokinetic/pharmacodynamic (PK/PD) profiles. Beta-lactams follow time-dependent killing kinetics, whereby efficacy is maximized when drug concentrations exceed the minimum inhibitory concentration (MIC) throughout a sufficient proportion of the dosing interval – a principle that supports extended or continuous infusion strategies in severe disease.

Glycopeptides such as vancomycin, as well as daptomycin and oxazolidinones like linezolid, are better characterized by the area under the concentration-time curve relative to the MIC (AUC/MIC), with AUC optimization being particularly important in enterococcal infections (34). Due to vancomycin's narrow therapeutic index, determining vancomycin serum concentration has become a standard of care to improve antibiotic therapy efficacy, reduce the risk of adverse reactions and lower costs. One study conducted in Cluj, Romania in 2025 concluded that continuous vancomycin infusion simplifies therapeutic monitoring by eliminating the need to precisely record start and end infusion times when collecting samples, so that AUC estimation during continuous infusion can be performed using a single random blood sample. Furthermore, evidence from the literature suggests that the risk of kidney damage during therapy appears to be lower with continuous *versus* intermittent administration, as well as near absence of infusion-related side effects (Red man syndrome) (35).

In contrast, aminoglycosides and fluoroquinolones exhibit concentration-dependent killing, where therapeutic success correlates with achieving high peak serum concentrations relative to the organism's MIC. These same PK/PD principles extend to the rationale for oral antibiotic therapy (OAT), supporting its capacity to maintain bactericidal activity and limit the risk of relapse when appropriately selected agents are used. They also explain why specific antibiotic classes are preferentially studied in clinical trials evaluating OAT as a step-down strategy in IE (34).

Oral Antibiotic Therapy – New Data

The POET (*Partial Oral Treatment of Endocarditis*) trial represents a paradigm shift in the IE management. This randomized, noninferiority, multicentre trial assigned 400 adults with stable left-sided IE to continue intravenous treatment or switch to oral antibiotic therapy after at least 10 days of intravenous antibiotics. The primary outcome (all-cause mortality, unplanned cardiac surgery, embolic events, or relapse of bacteraemia) occurred in 12.1% of the intravenously treated group versus 9.0% in the orally treated group, meeting noninferiority criteria (36).

Moreover, five-year outcomes demonstrated that oral step-down therapy reduced risks and showed a 35% reduction in mortality (26, 37). A pharmacokinetic sub study confirmed that target antibiotic levels were achieved in most patients receiving oral therapy, with probabilities of target attainment of 88 - 100% for amoxicillin and linezolid, and 71 - 100% for moxifloxacin and rifampicin. Patients with sub-target levels for one antibiotic were eligible for the administration of two different antibiotics (38).

Table II

Specific oral regimens used in the POET trial (36, 38, 39)

Oral regimen	Dosage	Susceptible bacteria
Amoxicillin + Moxifloxacin	1 g four times daily + 400 mg once daily	Streptococci, Enterococci
Dicloxacillin + Rifampicin	1 g four times daily + 600 mg twice daily	Staphylococci
Linezolid + Moxifloxacin	600 mg twice daily + 400 mg once daily	Staphylococci, Enterococci
Amoxicillin + Rifampicin	1 g four times daily + 600 mg twice daily	Enterococci

Eligible patients were adults (over 18 years of age) who fulfilled the Duke criteria for left-sided IE caused by one of the four qualifying pathogens (see below), in a stable clinical condition with a satisfactory response to initial IV antibiotic therapy for at least 10 days (or at least 7 days post-valve surgery). At the time of randomization patients had to have no active fever ≥ 38.0°C for at least 48 hours, show a decrease in biological inflammatory response (defined by C-reactive protein dropping to less than 25% of peak value or < 20 mg/L), and have a leukocyte count < $15 * 10^9$ during antibiotic treatment. Imaging studies also had to be performed within 48 hours before randomization, transoesophageal echocardiography (TEE) and transthoracic echocardiography (TTE) showing no abscess formation and no valve abnormalities requiring surgery. On the other hand, patients who were severely obese (with a BMI > 40 kg/m^2), those receiving antibiotic therapy for a concomitant infection, those with suspected gastrointestinal malabsorption and those expected to have reduced compliance were excluded from the study.

The trial only enrolled patients with left-sided IE caused by *Streptococcus spp.* (most common in patients enrolled in the study – approximately 49% of patients), *Enterococcus faecalis (*approximately 24% of patients), *Staphylococcus aureus (*approximately 22% of patients; methicillin-sensitive only**)**, coagulase-negative staphylococci (only 6% of patients).

Table III

Populations underrepresented or excluded from the POET trial and implications for clinical practice

Category	Population	Implications
Pathogen-related	Methicillin-resistant *Staphylococcus aureus* (MRSA)	No patients with MRSA were enrolled. Although oral agents such as linezolid and tedizolid exist, their efficacy as part of an oral step-down strategy was not studied
Pathogen-related	Fungal IE	Although oral azoles (e.g. voriconazole, fluconazole) have good bioavailability, *Candida* or *Aspergillus* IE typically mandates surgical valve replacement and prolonged IV antifungal therapy
Pathogen-related	Gram-negative IE	HACEK organisms, *Pseudomonas* spp., and Enterobacterales were not represented. Applicability of POET findings to these pathogens remains uncertain.
Pathogen-related	Culture-negative IE	Excluded because oral regimen selection required microbiological identification and susceptibility testing.
Clinical factors	Active abscess on TEE	Excluded because these patients generally require surgical evaluation.
Clinical factors	Valve abnormalities requiring surgery	Patients with a surgical indication were not eligible for oral step-down therapy.
Clinical factors	Persistent fever or marked inflammatory activity	Clinical stabilization was required before randomization.
Clinical factors	Severe immunosuppression	Results cannot be readily extrapolated to immunocompromised patients.
Clinical factors	Suspected gastrointestinal malabsorption	Adequate oral drug absorption was a prerequisite for enrolment
Clinical factors	Marked renal dysfunction	Not an explicit exclusion criterion, but renal impairment influences antibiotic dosing and may limit applicability.
Special populations	People who inject drugs (PWID)	Only five PWID were enrolled; results should be extrapolated to this population with great caution

Applicability to Prosthetic Valve Endocarditis (PVE)

PVE was not an exclusion criterion - 107 patients (27%) had a prosthetic valve involved, and 152 patients (38%) had undergone valve surgery before randomization (including 22 with prosthetic-valve endocarditis specifically). The subgroup analysis showed the odds ratio for the primary outcome in prosthetic *vs.* native valve patients was broadly consistent (OR 0.48 for prosthetic, 0.92 for native), and the interaction test was non-significant (p = 0.35). However, guidelines have traditionally been more conservative with PVE, given higher stakes and greater difficulty eradicating biofilm on prosthetic material. Patients with PVE who had signs of perivalvular extension or abscess were excluded.

Coagulase-negative staphylococci, a common PVE pathogen, had the highest primary outcome rate in the trial (40% in the IV group, 23% in the oral group),

likely reflecting frailty and comorbidity rather than treatment failure (38).

In clinical practice, most guidelines now accept oral step-down in stable PVE caused by the POET pathogens when strict criteria are met, but clinicians should remain cautious and administer individualized treatment.

The POET trial has also some limitations that restrict its broad applicability. Only about 20% of screened IE patients were enrolled, with exclusions for valve abscess, compliance concerns, need for future valve surgery, or ongoing signs of sepsis. The microbial spectrum was narrow: zero patients had MRSA and only 5 were persons who inject drugs (PWID) and prosthetic valve endocarditis was represented by only 22 patients, while right-sided IE accounted for roughly 10% of cases. Methodologically, outpatients in the oral arm were monitored 2 to 3 times *per* week and poorly compliant patients were excluded, reflecting conditions difficult to replicate in routine practice.

Concerns were raised about extrapolating these Danish findings to other healthcare systems, given the absence of MRSA and underrepresentation of intravenous drug users relative to IE populations elsewhere. These limitations are particularly relevant in the Romanian context, where *Staphylococcus aureus* accounts for 33% of IE cases and glycopeptide-based regimens are frequently required, and where drug use-associated IE is a growing concern, associated with high morbidity, mortality, and risk of reinfection, requiring multidisciplinary management beyond antimicrobial therapy alone. Also, in Romania, a large proportion of patients are culture-negative IE, and the criteria in the POET study would exclude a substantial proportion of Romanian IE patients, underlining the need for locally representative data before adopting oral step-down strategies. Another limitation would refer to the antimicrobial resistance which differs significantly across countries, and some of the anti-biotic regimens may not apply to different countries.

Despite these limitations, clinical implementation studies have confirmed feasibility and safety of these oral regimens. The Danish POETry study, a retrospective cohort study examined real-world implementation of oral step-down antibiotic therapy following the integration of the POET trial results into Danish clinical guidelines in May 2019. Among 562 eligible patients with left-sided IE caused by *S. aureus*, *E. faecalis*, *Streptococcus* spp., or coagulase-negative staphylococci, 240 (43%) were switched to oral therapy at a median of 16 days after treatment initiation, closely mirroring the 17-day median in the original POET trial. Oral regimens required a minimum of two antibiotic agents, chosen according to bacterial susceptibility and national guidelines derived from POET pharmacokinetic data, and side effects necessitating regimen change occurred in only 6% of patients. Oral step-down therapy was associated with a nearly 3-week reduction in hospital stay (24 *vs*. 43 days, $p < 0.001$) and a lower 6-month all-cause mortality (8% *vs*. 14%, $p = 0.024$). Critically, 28% of those switched to oral therapy did not fully meet the POET stabilization criteria, and this subgroup had markedly worse outcomes (22% *vs*. 9% primary outcome rate, $p = 0.004$), emphasizing the importance of adhering to established switching criteria (38).

Another study with real-world data from the Los Angeles County Department of Health Services showed similar outcomes between oral and intravenous-only therapy, with no significant difference in clinical success at 90 days or recurrence of bacteraemia. Patients treated with oral therapy had significantly fewer adverse events, supporting the feasibility of carefully selected oral therapy strategies in IE (40).

Another multicentre retrospective study is the ENDO-ORAL study, published in March 2026. This French multicentre retrospective cohort study evaluated the effectiveness of switching from intravenous (IV) to oral antibiotic therapy in 333 adults with IE treated between 2016 and 2023 at two tertiary centres. Patients were categorized into an exclusive IV group ($n = 233$) and an oral switch group ($n = 100$), with treatment failure defined as death, recurrence, or need for suppressive therapy within 90 days of completing antibiotics. A proportion of 44.7% of participants would have been ineligible for the landmark POET trial, including patients with right-sided IE, immunosuppression, or lack of standard microbiological documentation, making this cohort more representative of real-world complexity. The 100 eligible patients received an oral switch after a median of 16 days of IV therapy. Oral regimens consisted predominantly of a fluoroquinolone combined with rifampicin, clindamycin, or doxycycline for *Staphylococcus aureus*, and amoxicillin monotherapy for streptococcal IE, with a median oral treatment duration of 26.5 days.

According to the study, oral switch was not associated with increased treatment failure compared to exclusive IV therapy (HR = 0.55, 95% CI 0.27 - 1.17), and this was also applicable in the POET-ineligible subgroup. Patients who switched to oral therapy gained a median of 12 additional days alive outside hospital (59 *vs*. 47 days, $p = 0.001$), without a significant increase in adverse events. However, early oral switching, before 10 days of effective IV therapy, was associated with significantly worse outcomes (27.8% *vs*. 6.1% failure rate, $p = 0.006$), suggesting that adequate initial IV consolidation remains essential. Overall, these findings support broadening the use of oral switch therapy in IE, considering that the transition is not made too early (41).

An algorithm based on these cohort studies was imagined in the following manner, based on ESC guidelines 2023 and a review published in 2025 summarizing the studies based on oral step-down therapies (34).

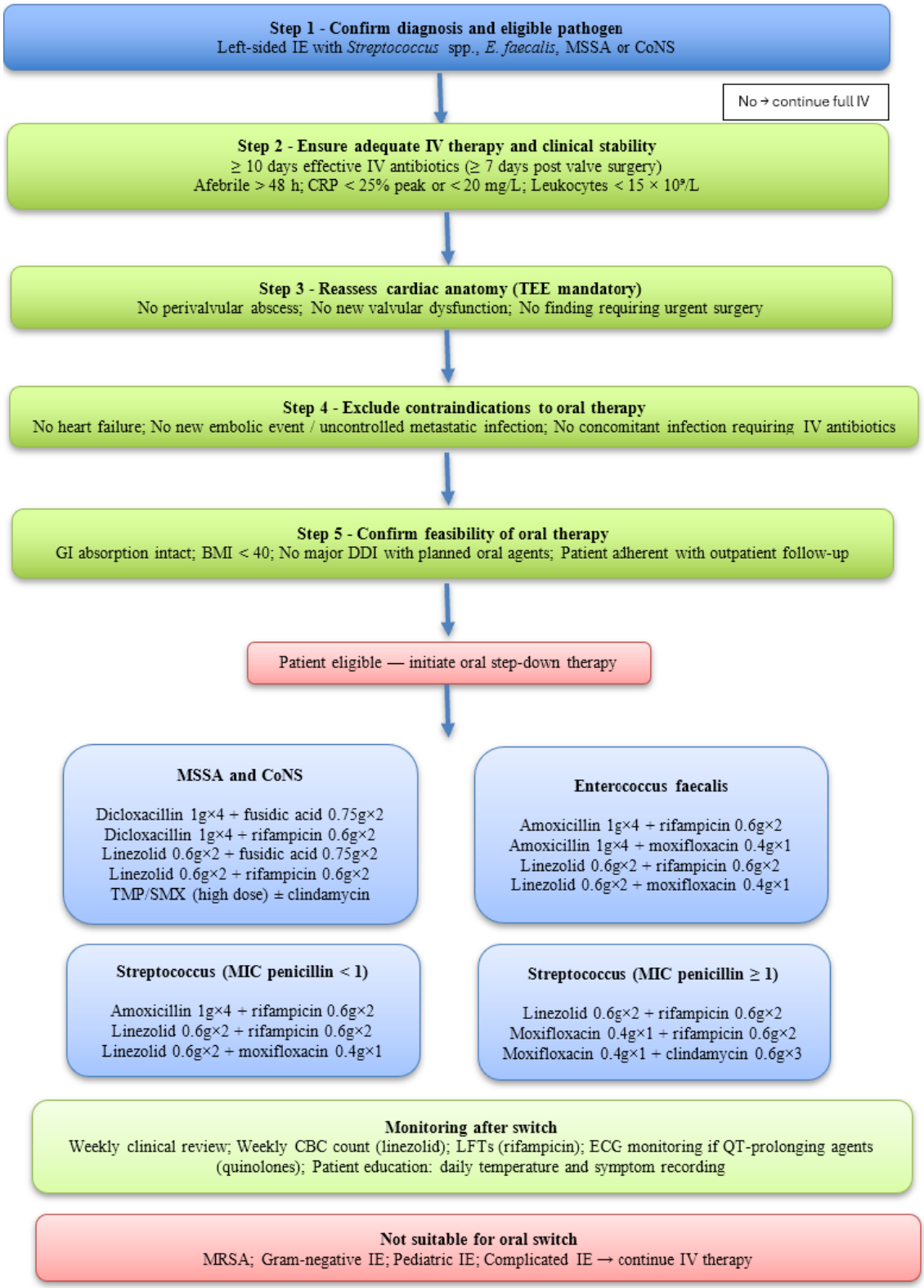

Figure 1.
Oral step-down therapy in left-sided IE – decision algorithm

Conclusions

New technological advances have allowed researchers to discover new pathogenesis mechanisms (the role of NET and proteomic involvement in vegetation formation), to better understand the mechanisms leading to IE and identify new therapeutic strategies beyond antibiotic treatment.

The most significant update in the management of IE is the validation of oral step-down antibiotic therapy for selected patients with left-sided IE.

The POET trial and further real-world studies (Danish POETry and ENDO-ORAL) have demonstrated that this approach is safe, effective, and associated with reduced hospital stays and potentially improved mortality, but has its own limitations.

From an antimicrobial stewardship perspective, further implementation of oral step-down strategies has multiple advantages: shorter IV exposure which reduces catheter-related complications, reduced nosocomial risks, reduced healthcare costs, while preserving antibiotic efficacy. Despite these advantages, increased caution has to be applied considering: premature switching, failure to meet stabilization criteria, and the use of a single oral agent.

These studies emphasize the need for individualized treatment decisions, ideally needing a multidisciplinary endocarditis team. Future trials are still needed to define the optimal timing, duration, and antibiotic combinations for oral therapy in populations excluded from clinical trials, including those with right-sided IE, prosthetic valve involvement, or complex comorbid profiles.

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Conflict of interest

The authors declare no conflict of interest.

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