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THERAPEUTIC ADVANCES IN INFECTIVE ENDOCARDITIS: NEW ANTIMICROBIALS, COMBINATION THERAPIES, AND CHALLENGES RELATED TO BIOFILM

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NARRATIVE LITERATURE REVIEW

ABSTRACT

Infective endocarditis remains a severe condition associated with high morbidity and mortality, prolonged hospitalizations, and the frequent need for a multidisciplinary approach. Despite the consolidation of classical antimicrobial regimens, recent years have brought new discussions on sequential therapies, long-acting antimicrobials, synergistic combinations, and strategies aimed at addressing biofilm, especially in infections caused by *Staphylococcus aureus*, coagulase-negative staphylococci, and enterococci. This study aimed to discuss therapeutic advances in infective endocarditis, with emphasis on new antimicrobials, combination therapies, and challenges related to biofilm. This is a narrative literature review based primarily on studies published between 2020 and 2026, retrieved from databases such as PubMed/MEDLINE, ScienceDirect, Springer, Scopus, and Web of Science. The findings indicate that drugs such as dalbavancin and oritavancin have been investigated as alternatives for therapeutic consolidation, particularly in selected and clinically stable patients. In addition, combinations such as daptomycin-ceftaroline have emerged as possibilities in persistent infections caused by resistant microorganisms. However, biofilm formation remains one of the main therapeutic obstacles, requiring integration between early diagnosis, appropriate antimicrobials, removal of infected devices, and eventual surgical intervention. It is concluded that therapeutic advances are promising, but still depend on robust evidence, clinical individualization, and integrated action by the endocarditis team.



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Keywords: Infective endocarditis; Antimicrobials; Biofilm; Combination therapy; Dalbavancin.

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1 INTRODUCTION

Infective endocarditis is a severe infection of the endocardium, frequently involving native heart valves, prosthetic valves, and intracardiac devices. Although it is considered a relatively uncommon condition, it has high lethality and requires rapid diagnosis, prolonged treatment, and integration among cardiology, infectious diseases, microbiology, and cardiac surgery (Delgado *et al.*, 2023; Rapti *et al.*, 2025).

In recent decades, epidemiological changes have modified the disease profile, with greater involvement of older patients, individuals with prosthetic valves, implantable cardiac devices, complex comorbidities, and previous exposure to invasive procedures. In this context, microorganisms such as *Staphylococcus aureus*, coagulase-negative staphylococci, streptococci, and enterococci remain among the main etiological agents, with different degrees of resistance and virulence (Imazio *et al.*, 2024; Kaushik *et al.*, 2024).

The treatment of infective endocarditis remains based on bactericidal antimicrobials administered for prolonged periods, with regimens adjusted according to the etiological agent, antimicrobial susceptibility, presence of prosthesis, and local or systemic complications. However, new antimicrobials, sequential therapies, supervised outpatient treatment, and synergistic combinations have been discussed as strategies to reduce therapeutic failures and prolonged hospitalizations (Iversen *et al.*, 2019; Pries-Heje *et al.*, 2022; Ashraf *et al.*, 2025).

In addition to antimicrobial resistance, biofilm constitutes a central challenge in the treatment of endocarditis, as it favors bacterial persistence, protection against the immune response, and lower antimicrobial penetration. Therefore, this study aimed to discuss therapeutic advances in infective endocarditis, with emphasis on new antimicrobials, combination therapies, and challenges related to biofilm (Lerche *et al.*, 2021; Kaushik *et al.*, 2024).

2 METHOD

This is a narrative literature review, an appropriate approach for critically discussing therapeutic advances, emerging trends, and clinical challenges in complex and continuously evolving topics. Unlike systematic reviews, the narrative review

allows for a broader and more interpretative analysis of scientific production, integrating guidelines, reviews, clinical studies, and observational evidence (Delgado *et al.*, 2023; Rapti *et al.*, 2025).

The search strategy was guided by the PICO framework: P : patients with infective endocarditis; I: new antimicrobials, combination therapies, and anti-biofilm strategies; C: conventional antimicrobial therapies; O: clinical improvement, microbiological eradication, reduction of recurrence, therapeutic safety, and biofilm control. Descriptors and combined terms were used, such as “infective endocarditis,” “antimicrobial therapy,” “dalbavancin,” “oritavancin,” “daptomycin,” “ceftaroline,” “combination therapy,” and “biofilm.”

Priority was given to articles published between 2020 and 2026, available in databases such as PubMed/MEDLINE, ScienceDirect, Springer, Scopus, and Web of Science, as well as recent international guidelines. Classic studies were also included when considered essential for understanding the topic, such as the POET trial on partial oral therapy in selected patients with stable infective endocarditis (Iversen *et al.*, 2019; Pries-Heje *et al.*, 2022).

3 RESULTS

The analyzed studies indicate that the treatment of infective endocarditis remains based on bactericidal antimicrobials, with duration varying according to the affected valve, etiological agent, and presence of prosthesis. The 2023 European guidelines reinforce the need for individualized therapy, multidisciplinary team evaluation, and early recognition of situations requiring surgical intervention (Delgado *et al.*, 2023; Imazio *et al.*, 2024).

Among recent advances, long-acting lipoglycopeptides stand out, particularly dalbavancin and oritavancin, which have been evaluated as alternatives for consolidation or sequential therapy in Gram-positive infections. Although they do not replace classical regimens in all patients, these drugs may be useful in selected contexts, especially when there is clinical stability, infection source control, and the need to reduce hospital stay duration (Suárez *et al.*, 2024; Aparicio-Minguijón *et al.*, 2025; Leanza *et al.*, 2025).

Another relevant area involves combination therapies, such as daptomycin associated with ceftaroline, especially in persistent infections caused by methicillin-resistant *Staphylococcus aureus* or coagulase-negative staphylococci. Although much of the data comes from observational studies and salvage therapy experiences, the therapeutic rationale is based on antimicrobial synergy, greater bactericidal activity, and potential impact on microorganisms adhered to surfaces. Next, the insertion of a summary table with the main findings of this study is suggested (Policarpo *et al.*, 2024; Kaushik *et al.*, 2024).

Table 1. Summary of Therapeutic Advances in Infective Endocarditis (2020–2026)

Therapeutic Strategy	Description	Main Evidence	Clinical Implications	Limitations/Challenges
Long-acting lipoglycopeptides (Dalbavancin, Oritavancin)	Antimicrobials with prolonged half-life allowing less frequent dosing and potential outpatient management	Observational studies and systematic reviews (Suárez <i>et al.</i> , 2024; Leanza <i>et al.</i> , 2025; Chaldoupis <i>et al.</i> , 2026)	Useful as sequential or consolidation therapy in clinically stable patients	Limited randomized trials; uncertainty regarding optimal dosing and long-term outcomes
Combination therapy (Daptomycin + Ceftaroline)	Synergistic antimicrobial approach targeting resistant Gram-positive pathogens	Observational studies and case series (Policarpo <i>et al.</i> , 2024; Kaushik <i>et al.</i> , 2024)	Potential option for persistent bacteremia and resistant infections (e.g., MRSA)	Increased cost, toxicity concerns, and lack of standardized protocols
Partial oral antibiotic therapy	Transition from intravenous to oral therapy in selected stable patients	Randomized clinical trial (POET) and follow-up studies (Iversen <i>et al.</i> , 2019; Pries-Heje <i>et al.</i> , 2022; Allaw <i>et al.</i> , 2025)	Reduces hospital stay and improves patient comfort when strict criteria are met	Requires strict patient selection, adherence, and close monitoring
Outpatient Parenteral Antibiotic Therapy (OPAT)	Administration of intravenous antibiotics outside hospital settings	Cohort studies and real-world evidence (Ashraf <i>et al.</i> , 2025)	Decreases hospitalization time and healthcare costs	Risk of complications, need for structured monitoring systems
Anti-biofilm strategies	Approaches targeting microbial biofilm, including pharmacological	Experimental and translational studies (Lerche <i>et al.</i> , 2021;	Potential to improve antimicrobial penetration	Mostly experimental; limited clinical applicability

	and experimental therapies	Pedersen <i>et al.</i> , 2024)	and reduce recurrence	
Multidisciplinary endocarditis team approach	Integrated management involving cardiology, infectious diseases, microbiology, and surgery	Clinical guidelines and observational data (Delgado <i>et al.</i> , 2023; Imazio <i>et al.</i> , 2024)	Improves outcomes, reduces mortality, and optimizes therapeutic decisions	Requires institutional structure and coordination
Surgical intervention	Removal of infected tissue or prosthetic material in complicated cases	Strong guideline-based evidence (Delgado <i>et al.</i> , 2023)	Essential in cases of abscess, prosthetic infection, or persistent bacteremia	Surgical risk, especially in high-risk patients

Source: Elaborated by the authors (2026), based on the main findings of the narrative literature review.

4. DISCUSSION

The discussion of therapeutic advances in infective endocarditis requires recognizing that the disease is not limited to the choice of an antimicrobial agent. It is a structural infection, often associated with vegetations, valvular destruction, embolization, abscess formation, and colonization of prosthetic materials. Therefore, therapeutic success depends on the combination of early diagnosis, appropriate antimicrobials, source control, and timely surgical evaluation (Delgado *et al.*, 2023; Imazio *et al.*, 2024).

Long-acting antimicrobials have gained interest as they allow treatment regimens less dependent on prolonged hospitalization or continuous intravenous access. Dalbavancin, for example, has a prolonged half-life and activity against Gram-positive organisms, which supports its use as sequential therapy in selected patients. However, its role should still be interpreted with caution, as much of the evidence derives from observational studies, retrospective cohorts, and reviews with clinical heterogeneity (Suárez *et al.*, 2024; Leanza *et al.*, 2025; Chaldoupis *et al.*, 2026).

Oritavancin has also been discussed in this context, particularly due to its spectrum against Gram-positive organisms and favorable pharmacokinetic profile. However, as with dalbavancin, there are still gaps regarding optimal dosing, treatment duration, patient selection, safety in complicated endocarditis, and direct comparison with conventional regimens. Therefore, these agents appear more promising as



consolidation therapy rather than universal substitutes for initial intravenous treatment (Gavaruzzi *et al.*, 2025; Goodman-Meza *et al.*, 2025).

Partial oral therapy, in turn, gained prominence after the POET trial, which demonstrated non-inferiority of switching to oral antibiotics in carefully selected patients with stabilized left-sided endocarditis. Long-term follow-up data reinforced this possibility; however, its application requires strict criteria, adherence, clinical stability, susceptible pathogens, absence of uncontrolled complications, and specialized follow-up (Iversen *et al.*, 2019; Pries-Heje *et al.*, 2022; Allaw *et al.*, 2025).

Combination therapies represent another important approach, particularly in persistent infections caused by resistant microorganisms. The association between daptomycin and ceftaroline has been described as a salvage alternative in persistent MRSA bacteremia and complex endovascular infections, with potential synergistic effects. However, it is not yet a universal strategy, as its indication must consider toxicity, cost, microbiological profile, and documented failure of conventional therapies (Policarpo *et al.*, 2024; Kaushik *et al.*, 2024).

Biofilm remains one of the main therapeutic challenges in infective endocarditis. In vegetations and prosthetic surfaces, microorganisms can organize into an extracellular matrix, reducing antimicrobial activity and favoring infection persistence. This condition partly explains the need for prolonged treatments, increased risk of relapse, and the indication for device removal or surgery in selected cases (Lerche *et al.*, 2021; Kaushik *et al.*, 2024).

Anti-biofilm strategies are still under development and include pharmacological, non-pharmacological, and translational approaches. Studies have explored the role of adjunctive therapies, agents capable of disrupting the extracellular matrix, bacteriophages, hyperbaric oxygen, and antithrombotic strategies; however, many of these alternatives remain experimental or supported by limited clinical evidence. Thus, biofilm management currently depends more on integrated therapeutic approaches than on a single pharmacological solution (Lerche *et al.*, 2021; Pedersen *et al.*, 2024).

In this context, the multidisciplinary endocarditis team plays a central role in decision-making. The choice between prolonged intravenous therapy, oral transition, outpatient treatment, long-acting lipoglycopeptides, antimicrobial combinations, or surgery must be individualized. Patients with abscess, hemodynamic instability,



recurrent embolization, infected prosthesis, or persistent bacteremia require more aggressive and early evaluation (Delgado *et al.*, 2023; Ashraf *et al.*, 2025).

Therefore, therapeutic advances in infective endocarditis do not imply abandoning classical regimens, but rather expanding the clinical repertoire. New alternatives may reduce hospital stay, facilitate outpatient care, and offer options for resistant infections, provided they are used judiciously. The contemporary challenge lies in balancing innovation, safety, scientific evidence, and real-world clinical practice (Rapti *et al.*, 2025; Chaldoupis *et al.*, 2026).

5 CONCLUSION

Therapeutic advances in infective endocarditis reveal a field in transformation, marked by the gradual incorporation of new antimicrobial options and individualized care strategies. Long-acting agents, combination therapies, and partial oral transition expand alternatives for selected patients, but do not eliminate the need for careful evaluation and specialized follow-up.

Biofilm remains a central obstacle, particularly in infections caused by *Staphylococcus aureus*, coagulase-negative staphylococci, enterococci, and cases involving prosthetic valves or intracardiac devices. Its presence favors bacterial persistence, therapeutic failure, and recurrence, reinforcing the importance of source control, removal of infected materials when indicated, and the integrated action of the endocarditis team.

It is concluded that the future of infective endocarditis treatment will depend on the combination of pharmacological innovation, robust clinical evidence, and individualized decision-making. Further prospective studies are needed to better define the role of dalbavancin, oritavancin, combination therapies, and anti-biofilm strategies, ensuring more effective, safe, and tailored treatments for complex patients.

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