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EMERGING TREATMENTS FOR INFECTIVE ENDOCARDITIS: THERAPEUTIC APPROACHES UNDER REVIEW

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ABSTRACT

Infective endocarditis (IE) is a serious clinical condition with a high mortality rate, especially if left untreated. This study presents a systematic review of the literature on emerging treatments for IE, addressing antimicrobial strategies and surgical interventions. The research included articles published between 2019 and 2024, using descriptors such as "infectious endocarditis". Modern antimicrobial approaches include the combined use of ceftriaxone and amoxicillin, as well as the transition to partially oral therapies in selected patients. Regarding surgical management, recommendations from international guidelines emphasize early interventions in cases of heart failure, persistent infection, or risk of embolization. Results point to the importance of a multidisciplinary approach, involving infectious disease specialists, cardiologists, and surgeons, in order to optimize outcomes and personalize treatments. Developments in guidelines for removal of implantable devices and for IE associated with cardiac interventions highlight the need for robust protocols and continued advances in the diagnosis and management of the disease.

Keywords: Infective Endocarditis. Treatment.

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INTRODUCTION

Infective endocarditis (IE) is a condition that affects the inner lining of the heart. The annual incidence rate ranges from 3 to 10 cases per 100,000 people, and the mortality rate can reach 30% in a 30-day period. The epidemiology of IE has undergone changes over time, with endocarditis associated with medical interventions now accounting for 25 to 30% of cases in contemporary individuals, a result of the increased use of intravenous catheters and cardiac devices. Currently, Staphylococcus aureus is the pathogenic agent most frequently found in IE cases, being involved in approximately 26.6% of them. Next, viridans group streptococci are responsible for 18.7%, other types of streptococci for 17.5% and enterococci for 10.5%. Together, these microorganisms account for 80 to 90% of endocarditis cases (Rajani and Klein 2020).

IE is a condition that, if left untreated, has a mortality rate of 100%. Although it has been a known disease since the nineteenth century, significant changes in its epidemiology have been noted, especially in recent years, following advances in diagnostic methods, which serve as the basis for this article (Østergaard et al., n.d.)element.

METHODOLOGY

The methodology of this study consisted of a systematic literature review on infective endocarditis. The research was conducted in the PubMed database, one of the main sources of scientific literature in the health area. Articles published between 2019 and 2024 were selected, ensuring the timeliness of the information. The descriptors used in the search were "infectious endocarditis", allowing the identification of relevant studies on the pathology.

After the initial search, the results were filtered to include systematic reviews, clinical studies and controlled trials, ensuring the quality of the evidence. In total, four articles were selected that met the inclusion criteria. These articles were read and analyzed for their relevance, methodology, and results. The information collected was organized in order to address the treatment and evolution of infective endocarditis.

This systematic approach made it possible to obtain a comprehensive view of infective endocarditis, contributing to the foundation of the study and to the discussion of its main clinical issues.

TREATMENT FROM INFECCIOSA ENDOCARDITIS

ANTIMICROBIAL TREATMENT

Infective endocarditis, which was fatal before antibiotics were introduced, requires the choice of an appropriate bactericidal antimicrobial regimen and the correct duration of treatment to ensure cure. The guidelines, based on clinical experience and cohort studies, show minimal variation in the recommended regimens for common organisms (Table 1) (Rajani and Klein 2020).

The use of ceftriaxone is growing as a synergistic agent in enterococcal endocarditis. European guidelines recommend the combination of amoxicillin and ceftriaxone, which is especially useful in patients with renal failure (Khaledi et al. 2022). In addition, partially oral treatment of endocarditis is gaining attention, with recent studies suggesting that this approach may be acceptable for highly selected patients (Rajani and Klein 2020).

For endocarditis caused by HACEK organisms (*Haemophilus* spp., *Aggregatibacter actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*), ampicillin should not be prescribed unless sensitivity is confirmed. Gentamicin is also no longer recommended due to its nephrotoxic risks (Khaledi et al. 2022). The standard treatment for HACEK is intravenous ceftriaxone monotherapy, given at doses of 2 g per day, for 4 weeks in cases of native valve endocarditis (NVE) and for 6 weeks in prosthetic valve endocarditis. For patients with β-lactam allergy, alternative options include fluoroquinolones such as levofloxacin, ciprofloxacin, or moxifloxacin (Rajani and Klein 2020).

In patients who have a microorganism that is highly sensitive to antibiotic therapy and who have an uncomplicated clinical presentation after treatment, outpatient parenteral antibiotic therapy (OPAT) may be considered. Hospital treatment is usually recommended in the first two weeks, when complication rates are highest. OPAT, via a long line, may be considered before this interval if patients are stable and if the infection is caused by a viridans group streptococcus or *by Streptococcus bovis* in a native valve. However, OPAT should be performed only with proper patient guidance, regular follow-up in post-discharge clinics, and ongoing clinical support (Rajani and Klein 2020).

Tabela 1. Regimes de tratamento recomendados para causas comuns de endocardite		
Organismo	**Válvula Nativa**	**Válvula protética**
Staphylococcus aureus (sensível à meticilina)	Flucloxacilina 2 g, 4–6 horas	Flucloxacilina 2 g, 4–6 horas por dia, e rifampicina 450–600 mg, bd, e gentamicina 1 mg/kg, bd (este último por 2–6 semanas)
Staphylococcus aureus (resistente à meticilina)	Vancomicina (com base no peso da dose)	Vancomicina (com base no peso da dose) e rifampicina 450–600 mg, bd, e gentamicina 1 mg/kg, bd (este último por 2–6 semanas)
Estreptococos do grupo Viridans e *Estreptococo bovis*	Penicilina benzilica 1,2 g, de 4 em 4 horas; ou ceftriaxona 2 g, uma vez ao dia (od); ou benzilpenicilina 1,2 g, de 4 em 4 horas e gentamicina 1 mg/kg, duas vezes ao dia (bd; ambos por duas semanas)	Penicilina benzilica 1,2 g, de 4 em 4 horas; ou ceftriaxona 2 g, od
Enterococo faecalis	Amoxicilina 2 g, de 4 em 4 horas, e gentamicina 1 mg/kg, bdouceftriaxona 2 g, bd	Amoxicilina 2 g, de 4 em 4 horas, e gentamicina 1 mg/kg, bd
Fonte. Tabela reproduzida de RAJANI, RONAK et al., 2020		

SURGICAL TREATMENT

Indications for surgical interventions are generally categorized into three groups: 1) development of heart failure, 2) difficulty in controlling infection, and 3) prevention of embolization caused by vegetation. These indications are uniform in international guidelines. The percentage of patients undergoing surgery during hospitalization ranges from 20 to 25% in population studies. There is considerable debate about the appropriate timing for surgery in IE cases, with discussions of early versus late surgery. A small, randomized study conducted in South Korea in 2012 looked at patients with left-sided IE who had vegetation larger than 10 mm. This study, which included 76 patients, suggested that early surgery was related to better overall outcomes, including reduced embolizations and deaths, compared with conventional treatment (Østergaard et al., n.d.)element.

Current guidelines establish class I recommendations for performing early or urgent cardiac surgery in cases of IE presenting with conditions such as acute heart failure, locally uncontrolled infection, IE caused by fungi or multidrug-resistant germs (MDR), as well as persistent vegetations greater than 10 mm in the left-sided heart valves, especially after an embolic event, even with adequate antimicrobial treatment. In addition, class IIa recommendations are made for situations of persistent bacteremia, despite appropriate therapy, in patients who have controlled septic embolism, especially in staphylococcus-infected prosthetic valves or non-HACEK gram-negative bacteria. Also included are those with very large vegetations, above 30 mm, or with severe valve defects and low operative risk (Rezar et al. 2021).

For patients with isolated vegetations in the mitral or aortic valves greater than 15 mm, without other surgical indications, an operative approach may be considered,

according to class IIb recommendations. In cases of ruptured intracranial emboli or infectious aneurysms, urgent cardiac and/or neurological surgery is indicated, provided there is no intracranial hemorrhage, severe comorbidities, coma, or severe neurologic complications following a stroke. Overall, the American Heart Association (AHA) guidelines do not differ significantly regarding the indication of early surgery (Rezar et al. 2021).

The American Association for Thoracic Surgery (AATS) guidelines also address the surgical treatment of IE, highlighting gaps in knowledge about the optimal timing for surgery. According to its 2016 guidelines, patients should be operated on within a few days of confirmation of the surgical indication, and earlier surgery should be considered for those at imminent risk of embolism, with a careful risk-benefit assessment, especially in patients with stroke or neurological complications (Rezar et al. 2021).

In addition, complete removal of leads from implantable cardiovert therapy (CIED) devices, including the generator, is recommended in patients with probable or confirmed CIED infection, as well as in cases of IE caused by *Staphylococcus aureus* or fungi, even in the absence of overt CIED infection. With regard to endocarditis after transcatheter aortic valve replacement (TAVR) or interventional valve repair, to date there are no official guidelines. The most important consideration in this context is to follow the guidelines available in the guidelines for endocarditis in prosthetic valves, especially for older and often weaker patients after mitral valve clipping, where a careful risk-benefit assessment should be performed before deciding on a surgical approach (Rezar et al. 2021).

DISCUSSION

Infective endocarditis (IE) is a complex condition that requires a multidisciplinary approach to treatment and management, given its high mortality rate when left untreated and the associated complications. Advances in knowledge about microbiology and antimicrobial treatment options have enabled better clinical outcomes. The appropriate use of bactericidal antibiotics, such as amoxicillin and ceftriaxone, in combination when necessary, has been widely supported by the existing literature. The growing acceptance of partially oral antimicrobial treatment also offers new perspectives for the management of patients recovering from IE, allowing for an effective transition from intravenous therapy to an outpatient regimen.

In addition to the pharmacological aspects, surgery plays a critical role in the treatment of IE, especially in cases complicated by heart failure or recurrence of infections. International guidelines provide a robust framework for surgical decision-making, emphasizing the importance of timing in intervention, where early surgery for patients with

large vegetations or high-risk conditions may result in better outcomes. This scenario blames the need for a deliberate commitment among the medical team to evaluate the MRI of each patient, since each case may present an individual risk profile.

It is also important to highlight the evolution in surgical indications for patients with implantable devices, such as cardioverting therapy devices, where removal is often necessary to eradicate the source of infection. Early identification and proper management are crucial to mitigate complications, which can include not only progression of infection but also embolization and structural damage to the heart.

CONCLUSION

The management of infective endocarditis continues to evolve as new evidence and research emerges in the field. Effective treatment requires a careful balance between appropriate antimicrobial therapy and timely surgical evaluation. The integration of diagnostic advances, such as the early detection of microorganisms and the analysis of vegetations, allows for a personalized approach that is increasingly vital to improve patient outcomes. The future of EI management lies in an ongoing collaboration between cardiologists, infectious disease specialists, and surgeons, focusing on evidence-based protocols that aim not only to treat the infection but also to optimize the recovery and quality of life of affected patients. Continuing education of health professionals and public awareness of the prevention and warning signs of IE are also essential to reduce the incidence and improve long-term outcomes.

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