ACTA MÉDICA PORTUGUESA
A Revista Científica da Ordem dos Médicos

Hospitalizations for Infective Endocarditis in Children: 15-Year Analysis

Internamentos por Endocardite Infeciosa em Idade Pediátrica: Análise de 15 Anos

Margarida DIAS✉[1], Rita AMORIM[1], Ana Luísa CORREIA[2], Marisa PEREIRA[3], Ana CORREIA-COSTA[3,4], Ana REIS-MELO[5,6], Margarida TAVARES[5]

Acta Med Port 2025 Jun-Jul;38(6-7):377-384 ▪ https://doi.org/10.20344/amp.22196

ABSTRACT

Introduction: Infective endocarditis (IE) is a challenging diagnosis with high morbidity and mortality. The aim of this study was to provide a comprehensive analysis of hospitalizations for infective endocarditis in pediatric population at a tertiary hospital.

Methods: A retrospective study examining hospitalizations for IE in pediatric population between 2008 and 2022 at Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE was conducted. Clinical presentation, treatment, complications, and outcomes of IE, as well as underlying microorganisms were reviewed.

Results: During this period, there were 27 hospitalizations for IE in children. In recent years, an increase in hospitalizations due to infective endocarditis has been observed, with the number fluctuating between zero and two per year from 2008 to 2017, and between one and five per year from 2018 to 2022. The mean age was 9.2 years (± 5.8), the length of hospitalization had a mean duration of 44 days (± 25.4) with a maximum of 113 days, and two deaths occurred. Heart disease was present in 88.9% (n = 24) of patients, of which 95.8% (23/24) was congenital, 59.3% (16/27) of the patients had prosthetic material and, of these, 18.8% (3/16) had a mechanical valve. Regarding diagnosis, 33.3% of patients had no vegetation in imaging tests. In 25.9% of cases, positron emission tomography was performed. Complications occurred in 51.9% of patients, with 44.4% having cerebral or pulmonary emboli. Regarding underlying organisms, *Staphylococcus aureus* (48.1%), *Staphylococcus epidermidis* (14.8%), and *Streptococcus* (14.8%) were the most frequent. One patient had a culture-negative IE. The mean duration of antibiotic therapy was 6.8 weeks, and 29.6% (8/27) underwent surgery.

Conclusion: Throughout the study period, our hospital observed a trend towards an increase in hospitalizations for infective endocarditis in the pediatric population. *Streptococci* are still described as the most prevalent etiology, but *Staphylococci* are known to become more frequent, as shown in our sample. Awareness of IE in patients with heart disease and implanted prosthetic material is crucial.

Keywords: Child; Endocarditis, Bacterial/complications; Endocarditis, Bacterial/diagnosis; Endocarditis, Bacterial/epidemiology; Hospitalization

RESUMO

Introdução: A endocardite infeciosa (EI) é um diagnóstico desafiante, com alta morbilidade e mortalidade. Este estudo teve como objetivo fornecer uma análise dos internamentos por endocardite infeciosa em idade pediátrica num hospital terciário.

Métodos: Foi realizado um estudo retrospetivo, que analisou internamentos por EI em idade pediátrica entre 2008 e 2022 no Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE. Foram revistos dados sobre a apresentação clínica, tratamento, complicações e evolução da EI, bem como os microrganismos envolvidos.

Resultados: Durante este período, ocorreram 27 internamentos por EI em crianças. Nos últimos anos, observou-se um aumento nos internamentos por EI, sendo que este número oscilou entre zero e dois por ano entre 2008 e 2017, e entre um e cinco internamentos por ano entre 2018 e 2022. A idade média foi de 9,2 anos (± 5,8), a duração média do internamento foi de 44 dias (± 25,4), com um máximo de 113 dias, e ocorreram duas mortes. A doença cardíaca esteve presente em 88,9% (n = 24) dos doentes, dos quais 95,8% (23/24) tinham doença cardíaca congénita. Dos doentes, 59,3% (16/27) tinham material de próteses cardíacas, sendo que 18,8% (3/16) possuíam válvula mecânica. Quanto ao diagnóstico, 33,3% dos doentes não apresentaram vegetações nos exames de imagem. Em 25,9% dos casos, foi realizada tomografia por emissão de positrões. Ocorreram complicações em 51,9% dos doentes, sendo que 44,4% apresentaram embolia cerebral ou pulmonar. Quanto aos microrganismos envolvidos, *Staphylococcus aureus* (48,1%), *Staphylococcus epidermidis* (14,8%) e *Streptococcus* (14,8%) foram os mais frequentes. Um doente teve EI com cultura negativa. A duração média da terapêutica antibiótica foi de 6,8 semanas, e 29,6% (8/27) dos doentes foram submetidos a cirurgia.

Conclusão: Verificou-se uma tendência para um aumento do número de internamentos por EI em idade pediátrica ao longo do período estudado no nosso hospital. Os estreptococos continuam a ser descritos como a etiologia mais prevalente, mas os estafilococos têm vindo a tornar-se cada vez mais frequentes, como demonstrado na nossa amostra. A consciencialização sobre a EI em doentes com doença cardíaca e material protésico implantado é fundamental.

Palavras-chave: Criança; Endocardite Bacteriana/complicações; Endocardite Bacteriana/diagnóstico; Endocardite Bacteriana/epidemiologia; Hospitalização

1. Department of Pediatrics. Centro Hospitalar Universitário de São João. Porto. Portugal.
2. Department of Pediatrics. Hospital Pedro Hispano. Unidade Local de Saúde de Matosinhos. Matosinhos. Portugal.
3. Department of Pediatric Cardiology. Centro Hospitalar Universitário de São João. Porto. Portugal.
4. Department of Gynecology-Obstetrics and Pediatrics. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.
5. Pediatric Infectious Diseases and Primary Immunodeficiencies Unit. Centro Hospitalar Universitário de São João. Porto. Portugal.
6. Biomedicine Department. Faculdade de Medicina. Universidade do Porto. Porto. Portugal.

✉ **Autor correspondente:** Margarida Dias. margarida.carvalhais.dias@ulssjoao.min-saude.pt

Recebido/*Received*: 16/08/2024 - **Aceite/*Accepted*:** 20/03/2025 - **Publicado/*Published*:** 02/06/2025

KEY MESSAGES

- The study observed a trend towards an increase in hospitalizations for infective endocarditis (IE) in children at a tertiary hospital.
- A significant majority of the pediatric patients (almost 90%) had underlying heart disease, with most of those cases being congenital heart defects, highlighting the link between heart disease and increased risk of IE.
- Staphylococcus aureus was the most commonly identified microorganism in infective endocarditis cases, with Staphylococcus epidermidis and Streptococcus species also being frequent causes.
- Awareness and early diagnosis of infective endocarditis, particularly in patients with congenital heart disease or implanted prosthetic material, are critical, as timely intervention, including antibiotic therapy, significantly impacts patient outcomes.
- The main limitations of this study included the fact that our findings may not be generalizable to other populations at risk, since our hospital is a referral center for pediatric cardiology, and the fact that Duke's criteria were not used and not all patients underwent the same diagnostic imaging tests available.

INTRODUCTION

Infective endocarditis (IE) remains a challenging diagnosis with high morbidity and mortality.[1,2] Despite improvements in health care, the incidence of infective endocarditis has not decreased over the past decades. This apparent paradox is explained by a progressive evolution in risk factors.[3-5] Many factors affect the outcome of this serious disease, including the virulence of the microorganism, characteristics of the patients, presence of underlying disease, and delays in diagnosis and treatment.

The epidemiology of pediatric IE has changed in the modern era. Currently, IE is most likely to occur among young children with complex congenital heart disease. Life-saving medical interventions like the use of implanted prosthetic material led to a higher incidence of these infections.[6,7]

Regarding disease-causing pathogens, *Streptococci* are described as the most frequent agent, but the incidence of *Staphylococci* is increasing. Furthermore, IE caused by *Staphylococcus aureus* is typically an acute fulminant process with a high mortality rate, as compared with IE caused by most of other pathogens.[8-10]

To help the clinical practice of professionals who treat these patients, a large number of guidelines to diagnose and manage IE have been developed in recent years by the European Society of Cardiology[11-14] as well as by other societies and organizations.[15-18]

The aim of this study was to provide a comprehensive analysis of all hospitalizations for IE in the pediatric population at a tertiary hospital, focusing on both epidemiological and clinical data. The clinical variables assessed included symptoms and signs at presentation, laboratory findings, underlying microorganisms, imaging results, treatment approaches, complications, and the overall outcome of IE. By evaluating these factors, this study seeks to enhance understanding of the disease's clinical course, its diagnosis and management in this tertiary hospital.

METHODS

We conducted a retrospective study examining clinical medical files of hospitalizations for IE in pediatric population between 2008 and 2022 at a tertiary hospital and referral center for pediatric cardiology: Centro Hospitalar Universitário de São João - Unidade Local de Saúde São João, EPE. Patients' demographic information, such as date of birth and age at hospitalization for IE, was collected. The patients' past medical history was also recorded, including underlying congenital heart disease, medical and surgical interventional treatment, and the presence of prosthetic material.

Clinical variables, like symptoms and signs at presentation, laboratory findings, underlying microorganisms, imaging results, treatment, complications, and outcome (recovery or death) of IE, were reviewed. We excluded cases of suspected infective endocarditis that were not confirmed.

A line graph was created to illustrate the evolution of the number of hospitalizations for infective endocarditis over the past 15 years. The horizontal axis represents the years, while the vertical axis indicates the number of hospitalizations.

Continuous variables are reported as mean and standard deviation. Categorical variables are mentioned as frequencies and percentages of the specific group.

Clinical and epidemiological data were obtained using the SClínico® and JOne systems. Statistical analysis was performed using IBM® SPSS® Statistics.

The data used in this study were anonymized, ensuring patient confidentiality and privacy.

RESULTS

During the study period, there were 27 hospitalizations

for IE in children. Its distribution is presented in Fig. 1. The mean number of hospitalizations per year was two, but there were years with no hospitalized patients for IE (2010, 2012, and 2016). On the other hand, the years 2018 and 2020 had the maximum number of hospitalizations (five per year, each). From 2018 onwards, there was a notable increase, with numbers ranging from one to five per year from 2018 to 2022 (*versus* from zero to two per year from 2008 to 2017).

Demographic and clinical characteristics are described in Table 1.

The length of hospitalization had a mean duration of 44.4 days (± 25.4) with a maximum of 113 days. Regarding discharge follow-up, 24 (88.9%) patients were discharged to the outpatient clinic, one (3.7%) was transferred to another hospital and two (7.4%) died during hospitalization.

The mean age of the patients was 9.2 years (± 5.8), the youngest patient was one month old and the oldest one was 17. Sixty percent of patients were female.

Considering risk factors for IE, heart disease was present in 88.9% (n = 24) of patients; 95.8% (23/24) had congenital heart disease, 59.3% (16/27) had prosthetic material and of these, 18.8% (3/16) had mechanical valves. Of the four patients that had structurally normal hearts, all had *S. aureus* IE, one had periungual wounds and three had no risk factors. A central venous catheter was present in 22.2% of the patients. One patient had a previous dental procedure. One patient, who had two hospitalizations for IE during the study period, had a primary immunodeficiency (DiGeorge syndrome).

Hospital-acquired IE occurred in 25.9% of the hospitalizations and community-acquired IE in 74%.

Fever was present in 24 (88.9%) of the patients and petechial rash/lesions were present in 22.2% of the patients. Other clinical presentations included chest pain, fatigue, vomiting, food refusal, dyspnea, and headache.

The distribution of the underlying organisms is presented in Table 2.

Staphylococcus was identified in 66.7% of patient cultures. *Staphylococcus aureus* was the most common species, found in 48.1% of cases. Among these, Methicillin-resistant *Staphylococcus aureus* (MRSA) was isolated in 18.5%, and Methicillin-sensitive *Staphylococcus aureus* (MSSA) in 29.6%. Additionally, *Staphylococcus epidermidis* was present in 14.8% of cases. *Streptococcus* species were found in 14.8% of cultures, including one case of *S. viridans* and three cases of *non-viridans* species. Other pathogens identified included *Listeria*, *Aspergillus*, *Candida*, *Klebsiella oxytoca*, *Granulicatella adiacens*, and *Cardiobacterium hominis*, among others. Four patients had isolation of more than one organism in culture: MRSA plus *S. epidermidis*, MRSA plus *Rothia mucilaginosa*, *S. epidermidis* plus *Candida parapsilosis*, and *S. hominis* plus *Klebsiella oxytoca* plus *Candida albicans*.

Diagnostic tests, treatment, complications, outcomes and follow-up are also described in Table 1.

Regarding diagnosis, blood cultures were positive in 96.3% of patients and four patients had a surgical fragment cultured (positive result in two). In the patient with negative cultures, the DNA of an *Aspergillus* was detected by reverse transcription polymerase chain reaction (RT-PCR) in blood samples/surgical fragment. Every patient did a transthoracic echocardiogram, nine (33.3%) did a transesophageal echocardiogram, 12 (44.4%) did computed

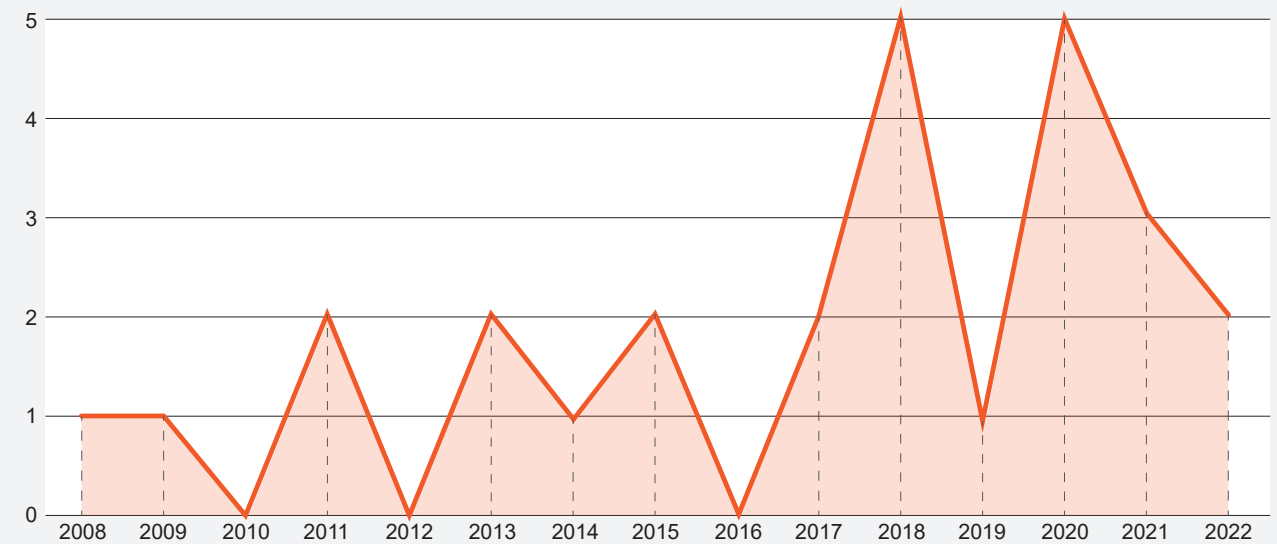

Figure 1 – Distribution of number of hospitalizations for Infective endocarditis per year (n = 27)

tomography (CT) and in seven (25.9%) cases positron emission tomography (PET) was performed. Almost half (42.8%) of the PET performed showed changes. In total, 33.3% (n = 9) of patients had no vegetation in imaging tests.

The mean duration of antibiotic therapy was 6.8 weeks, and 29.6% underwent surgery.

Complications occurred in 51.9% of patients, with 44.4% having cerebral or pulmonary emboli, 11.1% having brain abscesses, 8% having brain hemorrhage and 18.5% having liver, spleen, or kidney involvement. Among the cases with complications, in 64.3% of the patients, Staphylococci were isolated. On the other hand, in patients without complications, Staphylococci were isolated in nine (69.2%). Other agents isolated in cases with complications were *Aspergillus, Listeria, Cardiobacterium hominis, Candida albicans* and *Granulicatella adiacens*.

Table 1 – Demographic and clinical characteristics of hospitalizations for infective endocarditis (n = 27)

Age at hospitalization (mean, sd)	9.2 (5.8)
Sex (n, %)	
Male	11 (40)
Female	16 (60)
Length of hospitalization - days (mean, sd)	44.4 (25.4)
Clinical presentation[a] (n, %)	
Fever	24 (88.9)
Chest pain	2 (7.4)
Petechial rash/lesions	6 (22.2)
Risk factors[a] (n, %)	26 (96.3)
Heart disease	24 (88.9)
Prosthetic material	16 (59.3)
Mechanical valve	3 (11.1)
Central venous catheter	6 (22.2)
Wounds	6 (22.2)
Primary immunodeficiency	2 (7.4)
Dental procedure	1 (3.7)
Mode of acquisition of IE (n, %)	
Hospital-acquired IE	7 (25.9)
Community-acquired IE (n, %)	20 (74.0)
Medical complementary diagnostic tests[a] (n, %)	27 (100)
Blood culture	27 (100)
Positive blood culture	26 (96.3)
Transthoracic echocardiogram	27 (100)
Transesophageal echocardiogram	9 (33.3)
Computed Tomography	12 (44.4)
Positron Emission Tomography	7 (25.9)
Surgical fragment culture	4 (14.8)
Treatment[a] (n, %)	27 (100)
Antibiotherapy	27 (100)
Surgery	8 (29.6)
Mean duration of antibiotics in weeks (mean, sd)	6.8 (2.8)
Complications[a] (n, %)	14 (51.9)
Brain or pulmonary emboli	12 (44.4)
Brain abscess	3 (11.1)
Brain hemorrhage	2 (8.0)
Liver, spleen or kidney involvement	5 (18.5)
Arthritis	1 (4.0)
Discharge follow-up[b] (n, %)	
Outpatient consultation	24 (96)
Another hospital	1 (4)
Deaths (n, %)	2 (7.4)

IE: infective endocarditis; sd: standard deviation.
[a]: For clinical presentation, risk factors, diagnostic tests, treatment and complications, in the same variable, an individual may correspond to more than one category.
[b]: A total of 25 patients (with recovery) were included in this variable.

Table 2 – Infective endocarditis underlying organism (n = 27)

Organism	n (%)
MSSA	8 (29.6)
MRSA	5 (18.5)
Staphylococcus epidermidis	4 (14.8)
Staphylococcus hominis	1 (3.7)
Streptococcus viridans	1 (3.7)
Streptococcus sanguis	2 (7.4)
Streptococcus mitis	1 (3.7)
Haemophilus Parainfluenza	1 (3.7)
Listeria	1 (3.7)
Aspergillus spp	1 (3.7)
Granulicatella adiacens	1 (3.7)
Corynebacterium pseudodiphtheriticum	1 (3.7)
Rothia mucilaginosa	1 (3.7)
Candida parapsilosis	1 (3.7)
Candida albicans	1 (3.7)
Klebsiella oxytoca MS	1 (3.7)
Cardiobacterium hominis	1 (3.7)
Culture-negative IE	1 (3.7)

IE: infective endocarditis; MSSA: methicillin-sensitive *Staphylococcus aureus*; MRSA: methicillin-resistant *Staphylococcus aureus*.
Four patients had isolation of more than one organism in culture: methicillin-resistant *Staphylococcus aureus* (MRSA) plus *Staphylococcus epidermidis*, MRSA plus *Rothia mucilaginosa*, *Staphylococcus epidermidis* plus *Candida parapsilosis*, and *Staphylococcus hominis* plus *Klebsiella oxytoca* plus *Candida albicans*. Therefore, the total number in this table may exceed 100%.

The two deaths occurred after 11 days and 52 days of hospitalization, and the causative agents were *Aspergillus* and *Listeria monocytogenes*, respectively. Both patients had congenital heart disease. The patient with IE for *Aspergillus* had Down syndrome and a congenital atrioventricular septal defect with patch correction, without prosthetic material.

DISCUSSION

A trend towards an increase in hospitalizations for infective endocarditis in the pediatric population was observed throughout the study period at our hospital. Few studies of endocarditis in children are available. However, the incidence rate seems to be increasing, mainly the proportion of device-related IE (such as the use of implanted prosthetic material) due to the improvement in survival of patients with complex congenital heart disease.[4,5,7,19,20]

Patients with the highest risk of IE are those with congenital heart disease, predominantly if a prosthetic valve or prosthetic material is present. In fact, the majority of our patients had congenital heart disease and half of them had prosthetic material. In our sample, one patient who came from a developing country had rheumatic heart disease. Although in developed countries rheumatic heart disease is an uncommon predisposing condition for IE in children, in resource-limited settings, rheumatic heart disease remains an important risk factor.[21-23]

In our sample, 14.8% of the patients did not have heart disease and all of them had a *S. aureus* endocarditis. This result concurs with the literature, which reports that 8% to 10% of pediatric cases of IE occur in structurally normal hearts, most frequently associated with *S. aureus*.[24-26]

Patients with previous IE are known to have a greater risk of new IE, higher mortality and higher incidence of complications than patients with a first episode of IE.[27] In our study, only one patient had a history of IE and required intensive care during the second episode.

Regarding clinical presentation, unsurprisingly, fever was the most frequent symptom. The clinical presentation of pediatric IE is variable and depends upon the extent of the local cardiac disease, the degree of involvement of other organs (e.g., embolization), and the causative agent. Apart from the infectious process linked to IE, the inflammatory and immune response frequently plays a role in the associated symptoms and clinical findings.[28] Immunologic presentations (i.e., Janeway lesions, and Osler nodes) are less common in children than they are in adults, but this manifestation was present in 22.2% of our patients.

Regarding evaluation, one-third of our patients did not show vegetations in the imaging tests. However, only four of these patients underwent CT or PET scans. Of the five patients who did not perform these tests, all had structural heart disease with good quality images in the transthoracic echocardiogram.

The sensitivity and specificity of the modified Duke criteria for native valve endocarditis are both suboptimal, with acceptable sensitivity reported in previous studies, along with high specificity.[29] Diagnostic accuracy for intracardiac prosthetic material-related infection is even lower.[30] The 2015 infective endocarditis guidelines added the new imaging modalities of computer tomography (CT) and PET-computer tomography (PET-CT) into the diagnostic criteria and endorsed the concept of safety of relatively early surgical treatment.[4] The recent published 2023 European Society of Cardiology Guidelines for the management of endocarditis[14] added new recommendations regarding imaging techniques (class I, level of evidence B), such as: “cardiac CT angiography (CTA) is recommended in patients with possible native valve endocarditis” (NVE); “^{18}F-fluorodeoxyglucose PET/CT {[^{18}F]FDG-PET/CT} and cardiac CTA are recommended in possible prosthetic valve endocarditis (PVE)”; “Cardiac CTA is recommended in NVE and PVE to diagnose paravalvular or periprosthetic complications if echocardiography is inconclusive.”; and “Brain and whole-body imaging {CT, [^{18}F]FDG-PET/ CT, and/or MRI} are

recommended in symptomatic patients with NVE and PVE to detect peripheral lesions or add minor diagnostic criteria." Non-invasive imaging modalities could potentially improve the diagnosis of infective endocarditis; however, their diagnostic accuracy is unclear.[12] A systematic review[31] of diagnostic accuracy of imaging in infective endocarditis consistently found positive albeit weak evidence for the diagnostic benefit of [^{18}F]FDG-PET/CT and electrocardiogram (ECG)-gated multidetector CT angiography (MDCTA) after carrying out standard evaluation with transthoracic echocardiography and transesophageal echocardiography. The authors concluded that additional imaging techniques should be considered if the suspicion of infective endocarditis remains, such as leucocyte scintigraphy with SPECT/CT or magnetic resonance.

In our sample there was one culture negative IE, in which *Aspergillus* was detected by RT-PCR. *Staphylococcus* was the most frequent agent, followed by *Streptococcus*. In fact, *Streptococci* are still described as the most prevalent etiology in the literature but some studies have shown that epidemiological changes were marked by an increase in IE due to *Staphylococcus* and healthcare-associated IE, thereby highlighting the importance of non-specific infection control measures.[32,33] Kelchtermans *et al*,[10] evaluated the microbial profile of IE in children (53 patients in the sample) and the causative organism was found in 49 (92%) cases: viridans group *Streptococci* were identified in 32% of the cases, *S. aureus* in 25% and coagulase-negative staphylococci in 20%. On the other hand, in the Day *et al* study,[22] *S. aureus* was the most common organism (57%) followed by the viridans group of Streptococci (20%).

Granulicatella is associated with large vegetations (10 mm), higher rates of complications, and valve replacement (around 50%).[34] Actually, the patient in our sample in which this agent was isolated had complications (pulmonary embolism and pleural effusion) and underwent conduit and valve replacement.

In our sample there were two deaths, both in patients with congenital heart disease, one with IE due to *Aspergillus* and another with IE due to *Listeria monocytogenes,* with the understanding that multiple factors may have contributed to the outcomes. *Aspergillus* endocarditis represents the second etiological cause of prosthetic endocarditis following *Candida* spp.[35,36] However, our patient with *Aspergillus* endocarditis did not have prosthetic material. Endocarditis due to *Listeria monocytogenes* is a rare but serious disease, often leading to valve dysfunction and heart failure with high mortality.[37,38]

In our sample, most of the cases with complications occurred in patients in which staphylococci were isolated. Other agents isolated in cases with complications were *Cardiobacterium hominis, Candida albicans and Granulicatella adiacens*.

Hill EE *et al*[39] conducted a study in adult patients with IE, showing that factors significantly associated with any embolism were the community-acquired IE and the etiologic microorganism, in particular *Staphylococci a*nd nonviridans *Streptococci*.

An 11-year study (2000 - 2010) carried out in the USA in pediatric patients showed that, despite the significant decrease in Staphylococcal IE during the study period, this agent was associated with the highest mortality.[9] Although *Staphylococcus* was the most prevalent agent in our sample, both in the group without complications and in the group with complications, no deaths were caused by this organism.

The mortality rate in our study was 7.4%. Reported mortality rates among children with IE are unknown, ranging from one to five percent in some studies[9,22,40] and around 10% in congenital heart disease-associated IE.[6] A study[39] conducted in Belgium that included 53 pediatric patients showed a mortality rate of 13%. A prospective multicenter study[41] performed in Spain included 5590 pediatric and adult patients, and showed a pediatric mortality rate of 16.3% *vs* 25.9% in adults (p = 0.126). These data suggest that IE is still associated with relevant morbidity and mortality.

Our study has some limitations since our hospital is a referral center for pediatric cardiology and a tertiary hospital, and, therefore, our findings may not be generalizable to other populations at risk, and we could not determine population-based rates for pediatric IE. Other methodological limitations included: Duke's criteria were not used, since the practice in our hospital is to collect only one blood culture instead of two; and not all patients underwent the same diagnostic imaging tests available.

Therefore, an evidence-based diagnostic work-up for infective endocarditis, including non-invasive techniques, should be performed if infectious endocarditis is suspected. Novel approaches to imaging of the heart and extracardiac complications are needed to improve and individualize the diagnostic work-up, treatment, prognosis, and financial expenses in patients with suspected infective endocarditis.

In conclusion, this study observed a rising trend in hospitalizations for infective endocarditis (IE) in the pediatric population at a tertiary hospital. Nearly 90% of the children had heart disease, with the majority having congenital defects, underscoring the critical link between heart conditions and susceptibility to IE. *Staphylococcus aureus* emerged as the most commonly identified microorganism in these cases. These findings emphasize the importance of early awareness and diagnosis of IE, particularly in children with heart disease and implanted prosthetic material. Unexplained and persistent fevers without a potential source in a patient who carries a high risk for IE should

be evaluated thoroughly. Nevertheless, children without risk factors are also an important part of this condition.

ACKNOWLEDGMENTS

The authors gratefully acknowledge all participants of the present study for making it possible.

AUTHOR CONTRIBUTIONS

All authors contributed equally to this manuscript and approved the final version to be published.

PROTECTION OF HUMANS AND ANIMALS

The authors declare that the procedures were followed according to the regulations established by the Clinical Research and Ethics Committee and to the Helsinki Declaration of the World Medical Association updated in October 2024.

DATA CONFIDENTIALITY

The authors declare having followed the protocols in use at their working center regarding patients' data publication.

COMPETING INTERESTS

The authors have declared that no competing interests exist.

FUNDING SOURCES

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

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