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Epidemiological, Bacteriological, and Evolutive Features of Children Hospitalized for Infective Endocarditis in a Tertiary Tunisian Pediatric Department

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Abstract

Background: **Infective endocarditis is a rare condition in childhood, and there is limited data on this disease in Tunisia.**
Objective: **This study aims to analyze the epidemiological profile, bacteriological data, and prognosis of infective endocarditis in children admitted to the pediatric department of a University Hospital in Tunisia.**
Methods: **We conducted a comparative cross-sectional study in the pediatric department of Sahloul Teaching Hospital in Sousse, a tertiary referral hospital in Tunisia. The study included all children aged ≤ 18 years with infective endocarditis admitted to the tertiary referral center for pediatrics in Sahloul University Hospital from January 1994 to December 2022. The diagnosis of infective endocarditis was based on modified Duke's criteria.**
Results: **Thirty-six patients met the diagnostic criteria for infective endocarditis, resulting in a proportion of 07 cases per 1000 hospital admissions. The mean age was 6 years (range: 40 days to 16 years). Congenital heart disease was identified as the underlying lesion in 23 cases (63.9 %). Blood cultures were positive in 20 patients (55.6 %), predominantly with *Staphylococcus* species (55 %). The most frequent complications involved the central nervous system (8 cases; 22.2 %). The mortality rate was 25 %, and factors predicting mortality included heart failure on admission or during the hospital stay, increased leukocyte count, and decreased prothrombin time.**
Conclusion: **Our study reveals a shift in the prevalent underlying lesions, with rheumatic heart diseases no longer being the most common. *Staphylococcus* spp. emerged as the predominant organism in blood cultures. Notably, mortality predictors included heart failure, an elevated leukocyte count, and a decreased prothrombin time rate.**

Keywords: Infective endocarditis, Children, Echocardiography, Blood culture, Congenital heart disease

1. Introduction

Infective Endocarditis (IE) is an infection of the endocardium, particularly of the heart valves by bacteria or fungi. It occurs less commonly in children than in adults, and its incidence among the paediatric population seems to be rising [1]. In developed countries, the decline of rheumatic heart disease (RHD) and the gradual increase in the survival rate of children with congenital heart defects (CHD) have altered the epidemiology of IE in the paediatric population [2]. CHD currently represents the predominant underlying cause of IE in developed countries [2,3]. A recent report from the developing world indicated a decline in RHD and an increase in IE cases associated with CHD [4–6].

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In Tunisia, the clinical spectrum and the epidemiology of cardiac diseases have also evolved over the last three decades [7].

We have observed a decrease in the number of patients with RHD and an increase in patients with CHD. Additionally, antibiotic prophylaxis for potential septic procedures is not consistently prescribed, and late referral for surgery is common. These factors appear to influence the epidemiology data of IE in children in our country. In the Maghreb, and particularly in Tunisia, the epidemiological data of IE in children remains poorly documented.

To address this gap, our study analyzes the clinical profile, bacteriological data, and outcomes of IE in children admitted to the pediatric department of Sahloul University Hospital.

2. Materials and methods

2.1. Design and setting

We conducted a comparative cross-sectional study in the pediatric department of Sahloul Teaching Hospital in Sousse, a tertiary referral hospital in Tunisia. The study spanned from January 1, 1994, to December 31, 2022, with a median annual admission rate of approximately 1718 patients.

2.2. Study patients

All pediatric patients under the age of 18 diagnosed with definite or possible Infective Endocarditis and admitted to the department from January 1994 to December 2022 were included. The diagnosis of IE relied on the Modified Duke criteria, with patient identification facilitated through our hospital database using discharge diagnosis codes. Patients hospitalized for prolonged fever without meeting the Modified Duke criteria were excluded. In total, thirty-six patients met the diagnostic criteria for IE, resulting in a proportion of 07 per 1000 hospital admissions.

2.3. Definition of variables

For the diagnosis of IE, we applied the Modified Duke criteria as proposed by Li et al. [8]. This criteria set, used to assess our patients, comprises two major criteria and several minor criteria. To be enrolled in this study as definite IE, patients had to meet one of the following criteria: (1) the major two criteria; (2) one major and three minor criteria; (3) five minor criteria; or (4) histopathological evidence obtained surgically. Patients were classified as possible IE if they fulfilled one major and one minor criterion or three minor criteria.

Abbreviation

CHD	Congenital heart defects
IE	Infective Endocarditis
RHD	Rheumatic heart disease

2.4. Data collection

The medical records of each child were reviewed to determine their demographic data, preceding symptoms and illness, initial physical examinations, investigations, treatment, and outcome. All this information was collected for descriptive analysis. Primarily, age, gender, and underlying diseases of patients were studied. In the second stage, we detailed the clinical presentation of the patients, including temperature, hemodynamic status, cardiac auscultation, spleen enlargement, and a dermatological and neurological examination. Complementary biological examinations were reviewed; serum samples were analyzed focusing on the inflammation tests (C-reactive protein) and the complete blood count, urea, and creatinine. All patients had two to six sets of blood cultures that were done before the beginning of antibiotherapy. Serology was done where necessary. Trans-thoracic echocardiography data were also analyzed. Abdominal ultrasound, articular sonography, and other imaging reports were done when a complication was suspected. The medical or surgical treatment, the outcome of patients, and complications were also recorded.

2.5. Ethical considerations

This study received approval from the local Ethics Committee. All information pertaining to the identity of the patients was kept confidential.

2.6. Statistical analysis

The statistical analysis was conducted using the SPSS 10 software (IBM, Armonk, NY, USA). To assess variable distribution, the Kolmogorov–Smirnov test was performed. All continuous variables were found to be normally distributed and were presented as mean ± SD, while qualitative data were expressed as frequencies. Percentages and means were compared using the chi-square test and Student-t test, respectively. For multiple logistic

regressions, only variables with $p \leq 0.20$ in a univariate regression were included. Statistical significance was considered at $p < 0.05$.

3. Results

3.1. Patient characteristics

A total of 36 patients with a discharge diagnosis of IE were identified. Fifteen cases fulfilled the definition of possible IE, and 21 were definite IE. Among the patients, 22 were females (61.1 %). The mean age of the study population was six years old, with ages ranging from 40 days to 16 years. Only eleven patients were younger than two years old. A structural underlying CHD was reported in 23 cases (63.9 %), with 11 of them lacking surgical correction for their heart defects. The most common heart defect observed was ventricular septal defect (8 cases), followed by tetralogy of Fallot (4 cases). Rheumatic heart disease (RHD) was observed in seven cases (19.4 %). In six children (16.7 %), the heart was structurally normal. Among these, a 2.5-year-old girl had a history of nephroblastoma, which was treated with surgery and chemotherapy. Another female patient, 16 years old, was being followed for chronic renal failure. The remaining four patients were in apparent good health with no particular medical background.

3.2. Clinical examination

At the clinical examination, fever (88.9 %) and dyspnea (41.7 %) were the most prevalent presenting symptoms. A cardiac murmur was reported in 27 cases (75 %). Splenomegaly was observed in six cases (16.7 %), while hepatomegaly was present in 11 patients (30.6 %). Skin lesions were identified in three cases of IE (8.3 %), all presenting as purpura. An infectious portal of entry was recognized in eleven cases (30.6 %), with dental lesions in three cases, cutaneous lesions in two cases, pulmonary lesions in one case, and a urological lesion in one case. In two instances, IE occurred after cardiac catheterization, and two patients developed IE three days following cardiac surgery. Electrocardiography revealed heart block in two patients.

3.3. Laboratory findings

The complete blood count revealed anemia in 29 cases (80.6 %), increased white blood cell count in 30 children (83.3 %), and leukopenia in only one patient. C-reactive protein levels were elevated above 6 mg/L in 32 cases, ranging from 11 to 281 mg/L. Renal assessment was conducted for all patients, revealing the presence of acute renal failure in 11 cases (30.6 %) with a creatinine clearance ranging from 9.2 to 74 ml/1.73 m^2/min. The urine dipstick found hematuria and proteinuria in four cases (11.1 %) and three cases (8.3 %), respectively.

3.4. Microbiology

Blood cultures were conducted for all patients, with positive results in 20 cases (55.6 %). *Staphylococcus* spp. remained the predominant causative agent of IE, accounting for the majority of isolates (11 cases; 55 %) (see Table 1). None of the *Staphylococcus* isolates were methicillin-resistant. Gram-negative bacilli were identified in blood cultures from five cases. Among them, a multi-resistant strain was found in three cases: *Acinetobacter baumanii* in a patient diagnosed with IE 15 days after cardiac catheterization, *Pseudomonas aeruginosa* in a patient 20 days after truncus arteriosus repair surgery, and *Klebsiella pneumoniae* in a case three days after surgical correction of a ventricular septal defect. Negative blood cultures were observed in 16 patients (44.4 %), with 37.5 % (n = 6/16) of them having received antibiotics before arriving at our institution.

3.5. Echocardiography

Echocardiography was conducted for all cases within the first 72 h of hospitalization, revealing at least one vegetation in 32 cases (88.9 %). The size of the vegetation was precisely measured in 20 cases, with an average size of 8.6 mm (ranging from 3 mm to 30 mm). The mitral and aortic valves were the most frequent localizations, observed in 11 children (34.4 %) and 7 children (21.8 %), respectively. In five children (15.6 %), the vegetation was located on the right side of a pre-existing ventricular septal defect,

Table 1. Aetiologic agents of infective endocarditis (n = 36).

Isolated organism	Number of cases (%)
Staphylococcus aureus	10 (27.7 %)
Coagulase-negative staphylococci	1 (2.8 %)
Streptococcus spp.	1 (2.8 %)
Streptococcus sanguinis	1 (2.8 %)
Escherichia coli	1 (2.8 %)
Klebsiella pneumoniae	1 (2.8 %)
Acinetobacter baumanii	1 (2.8 %)
Pseudomonas aeruginosa	1 (2.8 %)
Gram-positive cocci (non identified)	2 (5.5 %)
Gram-negative bacilli (non identified)	1 (2.8 %)
Negative Culture	16 (44.4 %)

and in two patients, it was found on a tube connecting the right ventricular outflow tract to the pulmonary artery (see Table 2). Additional lesions discovered during echocardiography in our study population included a peri-annular abscess in 3 cases (8.3 %), perforation of the mitral valve in 2 cases (5.5 %), rupture of the mitral cordage in one case (2.8 %), a mycotic aneurysm in the ascending aorta in one case (2.8 %), and pericarditis in four cases (11.1 %). Mitral and/or aortic regurgitation were detected in 12 cases (33.3 %) (see Table 2).

3.6. Treatment and outcomes

All patients received therapy with at least two antibiotics, with the most common prescription being Cefotaxime associated with Amikacin (23 cases, 63.9 %). The mean duration of antibiotic therapy in our patients was 32 days. Notably, there was a significant increase in the use of vancomycin (13 cases, 36.1 %) despite the absence of resistant *staphylococci.*

Surgery was performed in 3 patients (8.3 %). The first patient underwent surgery for a peri-annular mitral abscess, also presenting with a complete atrioventricular block related to the cardiac abscess. The second patient underwent a double-valve replacement for mitral and aortic regurgitation. The third patient had a replacement of a right ventricle to pulmonary artery conduit.

The most common complication noted in our study was heart failure, diagnosed in 12 cases (33.3 %). Neurological complications were observed in eight patients (22.2 %) during their hospital stay, including ischemic stroke in 4 cases, cerebral hemorrhage in 2 cases related to the rupture of a mycotic aneurysm, and thrombophlebitis in one case. One case presented seizures and facial paralysis, suggestive of a cerebral stroke; however, cerebral imaging in this case was not conducted due to the critical condition of the patient, resulting in rapid death.

Other complications were diagnosed in 7 patients (19.4 %). Four patients experienced a pulmonary embolism, one patient had an aortic rupture complicating a mycotic aneurysm of the ascending aorta, one patient presented with pericarditis, and another patient had septic arthritis of the left knee. In the latter case, bacteriological analysis of the knee puncture revealed the presence of *Staphylococcus aureus*, the same bacteria found in the blood culture.

Recurrent IE was observed in one case. This baby initially presented with *P. aeruginosa* IE following truncus arteriosus repair surgery. Echocardiography showed a vegetation located on the tube connecting the right ventricular outflow tract to the pulmonary artery. The baby received antibiotic therapy with Ceftazidine and Amikacin for 4 weeks in the first onset. However, she experienced multiple recurrences of IE at intervals of between 3 weeks and 3 months. The non-replacement of the infected tube resulted in the non-eradication of the bacteria.

Mortality was observed in 9 (25 %) patients, with death attributed to various complications: septic shock (3 cases), neurological complications (3 cases), and cardiogenic shock (3 cases). To identify risk factors for mortality, a univariate analysis of key variables routinely associated with IE was conducted. The analysis revealed a high frequency of heart

Table 2. Echocardiograph findings.

Echocardiographic lesions			Number of cases (%)
Vegetation (32 cases)	Size of the vegetation (20 cases)	1–5 mm	6/20 (30 %)
		6–10 mm	10/20 (50 %)
		>10 mm	4/20 (20 %)
	Location of the vegetation	Mitral valve	11/32 (34.4 %)
		Aortic valve	7/32 (21.8 %)
		Right side of VSD	5/32 (15.6 %)
		Tricuspid valve	5/32 (15.6 %)
		Pulmonary valve	2/32 (6.2 %)
		RV-PA tube	2/32 (6.2 %)
		Others	5/32 (15.6 %)
Mitral regurgitation (mild to severe)			10 (27.8 %)
Aortic regurgitation (mild to severe)			4 (11.1 %)
Peri-annular mitral abscess			3 (8.3 %)
Perforation of the mitral valve in			2 (5.5 %)
Rupture of the mitral cordage in			1 (2.8 %)
Mycotic aneurysm in the ascending aorta			1 (2.8 %)
Pericarditis			4 (11.1 %)

VSD: ventricular septal defect; RV-PA tube: Right ventricule-Pulmonary artery tube.

Table 3a. The Univariate analysis of risk factors of death in patients with infectious endocarditis.

Characteristic		Died n (%) or median ± SD	Survivors n (%) or median ± SD	p-value
Age (months)		46.4 ± 53.2	81.4 ± 62.3	0,14
Gender	Male	3 (21,4)	11 (78,6)	1
	Female	6 (27.3)	16 (72.7)	
CHD	Yes	7 (30.4)	16 (69.6)	0,43
	No	2 (15.4)	11 (84.6)	
Neurological complications	Yes	4 (50.0)	4 (50.0)	0,08
	No	5 (17.9)	23 (82.1)	
Vascular complications	Yes	1 (20.0)	4 (80.0)	1
	No	7 (25.0)	21 (75.0)	
Heart Failure	Yes	6 (50.0)	6 (50.0)	**0,03**
	No	3 (12.5)	21 (87.5)	
Renal Failure	Yes	5 (45.5)	6 (54.5)	0,07
	No	2 (11.1)	16 (88.9)	
Staphylococcus aureus	Yes	2 (20.0)	8 (80.0)	1
	No	7 (26.9)	19 (73.1)	
Heart location	Left	5 (25)	15 (75)	1
	Right	3 (23)	10 (77)	
Fever duration		3.3 ± 2.0	4.5 ± 3.9	0,44
Hemoglobin g/dL		8.7 ± 1.7	10.3 ± 2.4	0,08
Leukocytes (Cells/mm^3)		25697.8 ± 18628.1	13866.7 ± 5408.2	0,09
Platelets (Cells/mm^3)		256333.3 ± 191411.2	277888.9 ± 128831.2	0,70
CRP (g/l)		137.0 ± 106.7	95.6 ± 85.6	0,24
PT		36.7 ± 15.9	77.9 ± 23.7	**0,001**
Creatinine Clearance		67.0 ± 37.6	123.4 ± 73.0	0,06
Dimension of vegetation		10.4 ± 11.3	8 ± 3.1	0,65
Ejection fraction		54.4 ± 8.7	55.1 ± 16.6	0,93

CHD: Congenital Heart Disease; CRP: C-Reactive Protein; PT: Prothrombin Time.

failure and a decreased prothrombin time rate as the only variables significantly associated with death in the study population (see Table 3a). In a multivariable analysis, heart failure on admission or during the hospital stay was found to be significantly associated with death in the study population (see Table 3b).

4. Discussion

While infective endocarditis (IE) is a rare condition in children, it remains a significant concern among pediatricians, with an estimated incidence between 0.34 and 0.64 cases per 100,000 per year [9]. In Tunisia, data concerning this disease is limited. However, our results indicate a notable proportion, estimated at 07 cases per 1000 hospitalizations. This elevated proportion may be attributed to the substantial pediatric population with heart diseases at risk of IE in our country, primarily congenital heart defects (CHD) and rheumatic heart disease (RHD).

Table 3b. Multivariate analysis of risk factors of death in patients with Infectious Endocarditis.

Factor	Adjusted OR	95 % CI	p
Heart Failure	7	[1.33–36.68]	0,021

A noteworthy finding in our study is the increase in the proportion of IE cases in children with CHD and a decrease in cases related to RHD. Several factors may contribute to this shift, including the decline of RHD in children due to the prompt diagnosis and management of beta-hemolytic streptococcal tonsillitis, improved diagnosis of CHD in our country, and the growing number of children with CHD undergoing cardiac surgery, especially palliative shunt procedures and intra-cardiac repairs with vascular grafts or patches. Delay in the surgical management of these children has led to the emergence of severe complications such as IE before complete surgical repair. Ventricular septal defect was the most common CHD complicated by IE in our study, consistent with findings in most published studies [5,10]. IE exhibits a bimodal distribution with peaks in infancy and adolescence [11]. In our study, similar to others, IE was found to be rare in infancy but frequently observed in children older than 2–3 years. The female predominance observed in our analysis contrasts with the similar frequency in male and female patients reported in most studies [4,5,12].

Blood cultures remain crucial for IE diagnosis. Microbiologically, the viridans group of *streptococci* and *S. aureus* dominate in pediatric IE [3,9,10,13]. *S.*

aureus, particularly, was the predominant pathogenic organism in our patients, consistent with previous studies. The frequent isolation of *S. aureus* and coagulase-negative *staphylococci* could be linked to the use of indwelling central venous catheters in critically ill children [14]. *S. aureus* is often introduced during surgery, with infections typically manifesting within 60 days after cardiac surgery; however, coagulase-negative staphylococci infections may present as late as ≥1 year after surgery [14]. Less frequently encountered microorganisms in pediatric IE include *Enterococcus* and the HACEK group of organisms (*Haemophilus species, Aggregatibacter species, Cardiobacterium hominis, Eikenella corrodens, and Kingella species*) [14]. In our study, the proportion of negative blood cultures was estimated at 47.1 %, which is higher compared to other studies. Notably, culture-negative IE accounted for 8 %–40 % of children clinically diagnosed with IE and negative blood cultures in several publications [1,5,15]. The elevated proportion of negative-culture IE in our study may be attributed to two hypotheses: firstly, the liberal prescription of antibiotics in febrile children, and secondly, the limited investigations conducted in our bacteriological laboratories. Molecular techniques, such as PCR, represent specific investigations that can detect bacterial DNA or the 16S subunit of bacterial ribosomes in patients with negative blood cultures [2,16].

Echocardiography remains a crucial tool in establishing the diagnosis of IE and stands as the most accurate imaging modality to identify endocardial lesions associated with this condition. Unlike the situation in adults, trans thoracic echocardiography is usually sufficient for children, with a positive yield in 80 % of IE cases [17]. In our study population, echocardiography identified vegetations in 91.2 % of cases, primarily involving the mitral and aortic valves. For cases involving complex CHD and prosthetic valve IE, where the initial echocardiographic analysis may be negative, positron-emission tomography emerges as a valuable tool for diagnosis confirmation, exhibiting a high level of sensitivity [2,17].

Despite advancements in medical therapy, IE in children remains a severe disease associated with high mortality and morbidity rates [9]. Thom et al. [9] demonstrated a mortality rate of 15 % and identified significant risk factors for mortality, including the presence of vegetations and heart failure. In a study by Tseng et al. [18], a mortality rate of 10.7 % was reported, with common risk factors being vegetations in both ventricles and prior use of broad-spectrum antibiotics. Our study observed a higher mortality rate of 23.5 %, which is notably elevated compared to developed countries [9,18]. Identified predicting factors for mortality in our cohort included heart failure, increased leukocyte count, and decreased prothrombin time rate. Heart failure, with an estimated frequency of 42–66 %, is the most common complication of IE, often caused by mitral and aortic valve lesions, and represents a primary indication for surgical intervention in IE [19]. In our study, the combination of heart failure, severe sepsis indicated by a high leukocyte count, and a decreased prothrombin level constituted a life-threatening condition leading to poor outcomes. Additionally, surgery in the acute onset of IE was associated with a high mortality rate.

4.1. Limitations

The primary limitation of our study lies in the relatively low number of patients and the retrospective design, which inherently carries the risk of incomplete data collection and evaluation.

5. Conclusion

Despite advancements in preventative and medical therapy in Tunisia, infective endocarditis (IE) remains a severe disease affecting children. Our study highlights a shift in the predominant underlying heart disease for IE, with rheumatic heart disease (RHD) no longer being the most common; it has been supplanted by congenital heart defects (CHD). Notably, *S. aureus* emerged as the predominant organism found in blood cultures of children with IE, suggesting a potential association with the overuse of antibiotics. Our findings underscore that heart failure, increased leukocyte count, and a decreased prothrombin time rate are critical predicting factors for mortality in pediatric IE. These results are likely correlated with the severe septic condition of patients, compounded by hemodynamic deterioration caused by heart failure. To further enhance our understanding of IE in Tunisia, additional population-based and multicenter hospital-based studies are warranted.

Author contributions

Conception and design of Study: HA, RH. Literature review: HA, RH, DBS, SM, FM, SN, SA, JC. Acquisition of data: HE, DBS, MBR, SM, FM, SN, LT, AT. Analysis and interpretation of data: HA, HE, MBR, LT, AT, SA, JC. Data collection: RH, HE, MBR, SM, FM, SN. Drafting of manuscript: HA, DBS. Revising and editing the manuscript critically for important intellectual contents: HA, LT, AT, SA, JC.

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The authors have non-financial interests to disclose.

Conflicts of interest

The authors declare that they have no competing interests.

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