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Behavior of infective endocarditis at the Pediatric Cardiocentro William Soler from 2000-2012

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ARTICLE INFORMATION

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Acronyms
ASD: atrial septal defect
CAVSD: complete atrioventricular septal defect
IE: infective endocarditis
PDA: patent ductus arteriosus
VSD: ventricular septal defect

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ABSTRACT

Introduction: Infective endocarditis is a rare disease in children. There are few publications that include large numbers of patients and discuss their risk fact.

Objective: To describe the clinical and epidemiological characteristics of pediatric infective endocarditis.

Method: A retrospective descriptive study was performed in the 33 patients admitted for infective endocarditis (who met the Duke criteria) at the Pediatric Cardiocentro William Soler in Havana, Cuba, from January 2000 to July 2012. Medical records were reviewed to obtain the primary data. Variables were stored and analyzed with SPSS version 15.0. Absolute and relative frequencies were determined and for the association between qualitative variables the Chi Square Test of Independence was used.

Results: Infective endocarditis predominated in female students (20/ 33 patients), the most frequent heart diseases were ventricular septal defect (50%) and tetralogy of Fallot (18.2%). Dental procedures (36.4% $p < 0.01$) and the use of intravascular catheters (36.4 % $p < 0.05$) were the most relevant risk factors. In 78.8 % of cases the presentation was subacute and in 57.6 %, nosocomial. Blood cultures were positive in 25 of 33 patients; in 14 of them (56 %) staphylococcal species were isolated. 46 complications were found, 30.4 % were congestive heart failure, followed by cerebral (21.8%) and lung embolisms, and pneumonia (10.9%).

Conclusions: Infective endocarditis was more frequent in children with congenital heart disease, and was significantly associated with defined risk factors, had a subacute clinical presentation and germ acquisition was nosocomial. Most common isolated germs were staphylococcal species and regarding complications heart failure and heart embolisms predominated.

Key words: Infective endocarditis, Pediatric age, Epidemiology, Diagnosis, Complications

Comportamiento de la endocarditis infecciosa en el Cardiocentro Pediátrico "William Soler" de 2000 a 2012

RESUMEN

Introducción: La endocarditis infecciosa es una enfermedad poco frecuente en niños. Existen escasas comunicaciones que incluyan gran número de enfermos y analicen

RESUMEN

Introducción: La endocarditis infecciosa es una enfermedad poco frecuente en niños. Existen escasas comunicaciones que incluyan gran número de enfermos y analicen sus factores de riesgo.

Objetivo: Describir las características clínico-epidemiológicas de la endocarditis infecciosa pediátrica.

Método: Se realizó un estudio observacional descriptivo retrospectivo en los 33 pacientes ingresados por endocarditis infecciosa (que cumplían los Criterios de Duke), en el Cardiocentro Pediátrico "William Soler" de La Habana, Cuba, desde enero de 2000 a julio de 2012. Se revisaron las historias clínicas para obtener el dato primario. Las variables fueron almacenadas y analizadas con el paquete estadístico SPSS versión 15.0. Se determinaron frecuencias absolutas y relativas y para la asociación de las variables cualitativas se empleó el estadígrafo χ^2 de independencia.

Resultados: La endocarditis infecciosa predominó en escolares de sexo femenino (20/33 pacientes), las cardiopatías más frecuentes fueron la comunicación interventricular (50 %) y la tetralogía de Fallot (18,2 %). Los procedimientos odontológicos (36,4 % $p < 0.01$) y el uso de catéteres intravasculares (36.4 % $p < 0.05$) fueron los factores de riesgo de mayor relevancia. En 78,8 % de los casos la forma de presentación fue subaguda y en 57,6 %, nosocomial. En 25 de los 33 pacientes los hemocultivos resultaron positivos y en 14 de ellos (56 %) se aislaron especies de *Staphylococcus*. Se registraron 46 complicaciones, 30,4 % correspondió a insuficiencia cardíaca congestiva, seguida de embolismo cerebral (21,8 %), pulmonar y neumonía (10,9 %).

Conclusiones: La endocarditis infecciosa fue más frecuente en niños con cardiopatías congénitas, y se asoció significativamente a factores de riesgo definidos, tuvo una presentación clínica subaguda y la adquisición del germen fue nosocomial. Los gérmenes más aislados fueron especies estafilocócicas y entre las complicaciones prevalecieron la insuficiencia cardíaca y los cardioembolismos.

Palabras clave: Endocarditis infecciosa, Edad pediátrica, Epidemiología, Diagnóstico, Complicaciones

INTRODUCTION

Infective endocarditis (IE) is a microbial disease of the endothelial surface of the heart (endocardium, valves or related structures) usually upon a previous injury. Its main anatomopathological manifestation is the vegetation, consisting of an amorphous mass of platelets and fibrin of variable size in the network of which numerous microorganisms and some inflammatory cells are trapped[1].

IE was first described in the mid-seventeenth century, and its infectious cause was determined two centuries later, with the identification of microorganisms within the vegetations[2,3]. In 1885, Osler made a clinical and pathological review of over 200 cases, and described in detail IE on the native valve, then called "malignant endocarditis", having a mortality of 100 %[4]. This study was extremely important at the time.

IE can be classified according to the temporal evolution of the disease, the site of infection, its cause or the presence of a predisposing risk factor[5,6]. Its diagnosis is made by clinical microbiological and echocardiographic criteria that have been modified over time.

According to Prado *et al.*[7] in 1981 Von Reyn and colleagues proposed some stringent diagnosis criteria based primarily on clinical and microbiological criteria. They distinguished three types of diagnosis: certain, probable and possible. Some limitations of this method were evident over the years, first only in a minority of patients it was possible to establish a certain diagnosis, secondly , new predisposing factors such as addiction to intravenous drugs were not taken into account, and third, the value of echocardiographic findings was not established either, therefore its application, although important at the time by laying the foundations of the diagnosis and treatment of IE, this classification prevented many cases from being diagnosed because the reduced sensitivity of its criteria.

In 1994, Durack and colleagues, according to Prado *et al*.[7] proposed a modification. Its advantages are the

inclusion, among the diagnostic criteria, addiction to intravenous drugs and echocardiographic findings, which with the rapid technological boom would achieve greater sensitivity without losing specificity. Thus the Duke criteria are set, which takes this name from the University where they were stated[7].

IE diagnosis is one of the most difficult in cardiology and it is not infrequently presented as fever of unknown origin, especially in children, which requires differentiating it from various rheumatologic and neoplastic diseases, especially leukemias and lymphomas. Clinical data are often nonspecific: fever, fatigue, weight loss or general malaise and other more specific symptoms, dependent on the site of infection: cutaneous, ocular, renal, vascular, mesenteric or cerebral[8-12].

IE is a rare disease in children, but its incidence has increased in relation to increased survival of patients with congenital heart disease and the increasing use of long-term vascular catheters, especially in preterm infants and patients with cancer[8-10,13].

The most common etiologic agents in children are Gram positive bacteria, including *Streptococcus viridans* and *Staphylococcus aureus*; among the less frequently isolated are: *Enterococcus sp.*, *coagulase-negative Staphylococcus*, *Streptococcus pneumoniae* and HACEK microorganisms (*Haemophilus influenzae*, *aphrophilus*, paraphrophilus; *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella sp*. and *Kingella kingae*). Endocarditis caused by Candida sp. and Gram-negative enteric bacilli are exceptionally observed[8,9,13-15].

The reported incidence rates range from 0.3 to 0.5% of patients admitted annually, with one case per 1,280 pediatric admissions per year and there are no differences by gender or race[11].

Experience in the diagnosis, clinical presentation and prognostic outcome of patients hospitalized with IE in a referral center, such as the William Soler Pediatric Cardiology Hospital as well as the lack of research that addresses this issue in our environment, motivated us to perform this study to describe the clinical and epidemiological characteristics of pediatric infectious endocarditis in patients admitted.

METHOD

Context and classification of the study

A descriptive, retrospective, observational study was performed in patients admitted with the diagnosis of IE in the William Soler Pediatric Cardiology Hospital in Havana, Cuba, from January 2000 to July 2012.

Universe and Sample

The 33 patients admitted for IE in the study period, who comprehensively fulfilled the Duke criteria for the disease, according to data collected from the medical records, were included in the study.

Variables studied

The variables studied were age, sex, presence of congenital heart disease, risk factors (history of oral sepsis or dental procedure), and the use of deep venous access routes. The acute or subacute clinical condition and the possible source of infection were determined according to the clinical characteristics of patients. The most common causes of IE and presented complications were defined according to the results of complementary tests performed.

Techniques for collecting, processing and analyzing information

The medical records of each patient were reviewed with prior authorization from the hospital directors. The variables obtained were stored and analyzed using SPSS statistical software, version 15.0. Absolute and relative frequencies were determined, for the association of qualitative variables using contingency tables, the statistic χ^2 of independence with its associated p significance was used ($p > 0.05$ there is no significant association and for $p < 0.05$, there is).

Bioethical considerations

Although no patient or family information is required, the research met the required five ethical principles, respect for persons, beneficence, non-maleficence, justice and autonomy, which ensured the strict data confidentiality.

RESULTS

Table 1 shows the distribution of patients with IE by age group and sex, the most affected group was 5 to 19 years with 15 patients (45.5%) followed by children under 1 year and the group from 1 and 4, with nine patients each (27.3%). With regard to gender, there was a predominance of female patients, 20 cases (60.6 %).

The distribution of different types of congenital heart disease (**Table 2**) shows that in 22 of the 33 patients

studied there was a birth defect. The ventricular septal defect (VSD) in 11 (50%), followed by tetralogy of Fallot in 4 cases (18.2%). The rest, (ASD, CAVSD, aortic valvular and subvalvular stenosis and PDA) had of low prevalence.

Table 1. Distribution of patients by age group and sex.

Age group	Sex				Total	
	Female		Male			
	N°	%	N°	%	N°	%
Less than 1 year	4	20,0	5	38,5	9	27,3
1 – 4 years	6	30,0	3	23,1	9	27,3
5 – 19 years	10	50,0	5	38,4	15	45,4
Total	20	60,6	13	39,4	33	100

Table 2. Distribution of patients according to the type of congenital heart disease.

Type of Heart Disease	N°	%
ASD	1	4,5
VSD	11	50,0
CAVSD	2	9,1
Aortic stenosis	2	9,1
Subvalvular aortic stenosis	1	4,5
Tetralogy of Fallot	4	18,2
PDA	1	4,5
Total	22	100

ASD: atrial septal defect, VSD: ventricular septal defect, CAVSD: complete atrioventricular septal defect, PDA: patent ductus arteriosus

Table 3. Distribution of patients, according to the presence of risk factors and disease.

Heart disease	Risk factors				Total	
	No		Yes			
	N°	%	N°	%	N°	%
No	5	71,4	6	23,1	11	33,3
Yes	2	28,6	20	76,9	22	66,7
Total	7	21,2	26	78,8	33	100

$\chi^2 = 5.802$; $p < 0.05$

From a total of 26 patients (78.8%) with some risk factor for IE, 20 were cardiac patients (76.9 %), representing a significant association ($p < 0.05$) between the presence of congenital heart disease andrisk factors (**Table 3**).

In 12 patients (36.4%) a history of oral sepsis and previous dental procedures was demonstrated (**Table 4**), 1 of them (8.3%) in the group of 1-4 years and the rest (91, 7%) 5 to 19 years, an age group that showed a statistically significant difference ($p < 0.01$).

In Table 5 patients with IE and a history of intravascular catheters use are distributed according to age groups. The group of patients younger than 1 year was the most affected with 7 of 9 cases, accounting for 58.3 % of the 12 where intravascular devices were used, so the difference was statistically significant.

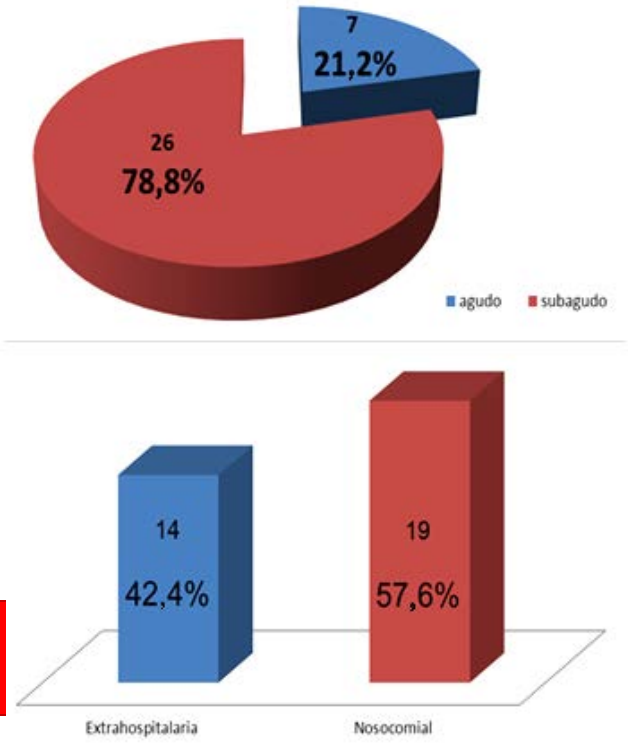

Figure 1. Distribution of patients by clinical course and the infection source.

Figure 1, top panel, shows that the predominant clinical course in the IE of these patients was subacute

Table 4. Distribution of patients with oral sepsis and dental procedures, according to age groups.

Age groups	Previous oral sepsis and dental procedures				Total	
	No		Yes			
	N°	%	N°	%	N°	%
Under 1 year	9	42,9	0	0,0	9	27,3
1 - 4 years	8	38,1	1	8,3	9	27,3
5 - 19 years	4	19,0	11	91,7	15	45,5
Total	21	63,6	12	36,4	33	100

$\chi^2 = 16.483$; $p < 0.01$

Table 5. Distribution of patients with a history of intravascular catheter use, by age groups.

Age groups	Intravascular catheter use				Total	
	No		Yes			
	N°	%	N°	%	N°	%
Under 1 year	2	9,5	7	58,3	9	27,3
1 - 4 years	7	33,3	2	16,7	9	27,3
5 - 19 years	12	57,1	3	25,0	15	45,5
Total	21	63,6	12	36,4	33	100

$\chi^2 = 9.184$; $p < 0.05$

Table 6. Distribution of patients by complications.

Complications	N°	%
Heart failure	14	30,4
Pulmonaryembolism	10	21,8
Cerebral embolism	5	10,9
Pneumonia	5	10,9
Acuteaorticregurgitation	4	8,7
Septic Shock	2	4,3
Arrhythmias	2	4,3
Renal embolism	2	4,3
PDA rupture	1	2,2
Aneurysm of sinus of Valsalva	1	2,2
Total	46	100

sepsis (78.8%), and in the lower, the nosocomial source of infection predominated (57,6 %).

Blood cultures (**Figure 2**) were positive in 25 patients (75.8%), in which, most often, coagulase-negative *Staphylococcus* (32 %), coagulase-positive (24%) and *Streptococcus viridians* species were isolated (20 %).

46 complications were found, which suggests that there were patients who had more than one (**Table 6**). In 14 heart failure was diagnosed, representing 30.4% of all complications, 10 had pulmonary embolism (21.8 %) and 5 (10.9%), cerebral embolism and pneumonia, respectively. Considering embolic events in their entirety (pulmonary, brain and kidney) they prevail over heart failure.

DISCUSSION

The distribution of cases by age resembles the bimodal distribution found by Day *et al*[16] in 1,588 cases, with peak incidence in infants and in patients older than 17 years. No explanation for the behavior of the group of 1-4 years with also 9 patients is found.

Other studies do not describe this kind of behavior and show predominance in infants[17]. The rest of the studies reviewed, show mean ages ranging between 5.8 and 8.6 years [9,18].

With regard to gender, in this series there was a predominance of IE in female patients, which coincides with the findings of Marom *et al*.[10] in Israel and Bitar *et al*.[12] in Lebanon.

In the distribution of the different types of heart disease, it is noteworthy that in 22 of the 33 patients a congenital defect is presented, which is consistent with multiple studies that reaffirm this precedent (antecedent) as the main predisposing factor of IE in children. Authors such as Johnson *et al*.[20], in a review of 60 years at the Mayo Clinic found a VSD in 35% of patients with IE and Niwa *et al*.[15] report that VSD as lonely heart disease was present in 37, 5% of their patients so it was the most prevalent, however, as a whole, cyanotic congenital heart diseases were more frequent. Meanwhile Bittar *et al*.[12] point to tetralogy of Fallot and pulmonary stenosis as the heart diseases of greater significance.

Saxena *et al*.[21], found congenital heart diseases in 17 of the 19 cases studied and of these, there was

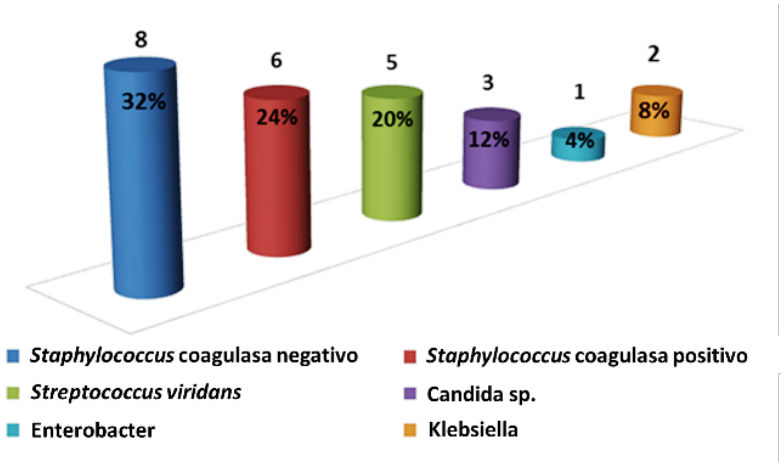

Figure 2. Distribution of patients by germ isolated in blood cultures.

another risk conditionin 10. In a study by Valente *et al*.[22], in 9 of the 10 cases with IE in their series, presented congenital heart disease with prevalence of two factors: the use of deep venous catheters (7 cases) and recent surgery of the heart disease in 5. Prematurity was also studied which was not considered in this study. Sadiq*et al*.[19] reported 45% of cardiac malformations, in contrast with 53 % of rheumatic heart disease, and a history of previous cardiac surgery was found in 4 patients.

In the research of Niwa et al.[15] predisposing conditions also prevailed in patients with cardiovascular malformations and for authors like Casanova[23], the source of bacteremia is found in two thirds of patients, with dental procedures and surgery as the major sources.

The risk of bacteremia after dental extractions is 60 %, after periodontal surgery 88%, and after tonsillectomy, 35 %[11,24]. For multiple authors, the most outstanding, among the many causes of bacteremia, are oral sepsis and dental procedures which can reach up to 46 % of potential bacteremia[15,25].

The distinctive features of risk factors for IE in infants are recognized, and it is argued that in this age group prematurity, immunosuppression, and use of deep venous catheters prevail[26,27], thus differing from the other age groups.

For Valente *et al*.[22] the use of intravenous catheters and its relationship to bacteremia (73%) was very prevalent and although the primary objective of the study was not IE, but Staphylococcus aureus bacteremia, the percent of patients who developed bacteraemia in relation to the use of catheters was significant, as there were 10 cases of IE, of which 7 used catheters; besides the *Staphylococcus aureus* germ was isolated in all cases.

The literature consulted about this theme states that IE is presented as an important toxinfectious state, however in most cases it manifests with nonspecific symptoms and signs of long duration, that when assessed by other specialists, they are considered as other conditions such as autoimmune, rheumatologic, and tumoral[24,28,29].

Ishiwada *et al*.[13] observed a direct relationship between the causal microorganism and the clinical profile of IE with difference in the typical acute toxinfectious presentation produced by coagulase-positive *Staphylococcus* from the dependent subacute form of the rest of the microorganisms isolated in their work; and in Peña *et al*.[30] series the subacute presentation was predominant, but the main cause of death was acute heart failure.

In the series of Marom*et al*.[10], a substantial prevalence of IE from nosocomial source in 30 of their 51 cases (59%) was not reported. Similar behavior is described in the research conducted at the Stollery Children's Hospital where out of 31 cases studied, 19 had nosocomial acquisition of IE[31]. Other authors have found much lower frequencies of nosocomial infection with only 10% in their respective series, half of them associated with intravascular devices[31,32].

In this series, besides the use of intravascular catheters, recent cardiovascular surgery was presented in 11 cases, so these two variables combined could explain the slightly higher incidence of nosocomial IE. This result is interesting and differs from that of most authors that place *Staphylococcus aureus* (coagulase-positive) and *Streptococcus viridans* as the bacteria most frequently isolated from blood cultures of patients with IE[9,10,14,16-18]. Others have found a predominance of coagulase-negative Staphylococcus and associate it with prosthetic valve IE or with cardiovascular surgery[1,33,34].

The fact that in our series only 1 case of prosthetic valve IE was found is attributed tothe fact that there were 11 reconstructive cardiovascular surgeries in patients with congenital malformations.

It is noteworthy to point out theclear trend of the

prevalence of *Staphylococcus aureus* IE both on native as on prosthetic valve, which was traditionally thought to be caused by *Staphylococcus epidermidis* (coagulase negative)[4,35].

The complications of IE are numerous and many authors classify them into two groups: intra and extracardiac[12,13]. Within the first group we have congestive heart failure, intracardiac fistulae and abscesses, hemopericardium, cardiac tamponade, valvular insufficiency and fracture or rupture of sinus of Valsalva , while in the second group emboli at different levels (renal, neurological, pulmonary, spleen), as well as autoimmune phenomena[9,14,15]. In this sense, our results are consistent with those of other authors[15,28,36,37], who consider the left ventricular failure as the first among the complications of IE due to valve disease, which causes hemodynamic disorders. Ferrieri[6] and Paganini[18] also agree that the ventricular dysfunction is the most common complication associated with *Staphylococcus aureus* infection and also constitutes a common cause of surgery[6,18]. Schroth *et al.*[37] reported 6 cases of pulmonary embolism in 11 patients with IE in their series; for Knirsch and Nadal[38] pulmonary and brainembolic phenomena accounted for 33 and 28% respectively, while Hoyer and Silberbach[39] consider that pulmonary embolism occurs in 10% of cases of IE in pediatric age, exceeded in frequency by valvular insufficiency and surgical complications. Another group of authors[8], with whom we disagree, look down on pulmonary embolism as a complication of importance.

CONCLUSIONS

IE predominated in female students with VSD and tetralogy of Fallot as underlying congenital heart diseases. Dental procedures and the use of intravascular catheters had a significant association with IE. Subacute clinical presentation and nosocomial infection were predominant, as well as the isolation of staphylococci species in blood cultures. Congestive heart failure and embolic phenomena were the most important complications.

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