

## CLINICAL RESEARCH ARTICLE



# Infective endocarditis in children and adolescents: a different profile with clinical implications

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**BACKGROUND:** Our aim was to compare pediatric infective endocarditis (IE) with the clinical profile and outcomes of IE in adults.

**METHODS:** Prospective multicenter registry in 31 Spanish hospitals including all patients with a diagnosis of IE from 2008 to 2020.

**RESULTS:** A total of 5590 patients were included, 49 were <18 years (0.1%). Congenital heart disease (CHD) was present in 31 children and adolescents (63.2%). Right-sided location was more common in children/adolescents than in adults (46.9% vs. 6.3%,  $P < 0.001$ ). Pediatric pulmonary IE was more frequent in patients with CHD (48.4%) than in those without (5.6%),  $P = 0.004$ .

*Staphylococcus aureus* etiology tended to be more common in pediatric patients (32.7%) than in adults (22.3%),  $P = 0.082$ . Heart failure was less common in pediatric patients than in adults, due to the lower rate of heart failure in children/adolescents with CHD (9.6%) with respect to those without CHD (44.4%),  $P = 0.005$ . In-hospital mortality was high in both children, and adolescents and adults (16.3% vs. 25.9%;  $P = 0.126$ ).

**CONCLUSIONS:** Most IE cases in children and adolescents are seen in patients with CHD that have a more common right-sided location and a lower prevalence of heart failure than patients without CHD. IE in children and adolescents without CHD has a more similar profile to IE in adults.

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### IMPACT:

- Infective endocarditis (IE) in children and adolescents is often seen in patients with congenital heart disease (CHD).
- Right-sided location is the most common in patients with CHD and heart failure is less common as a complication compared with patients without CHD.
- Infective endocarditis (IE) in children/adolescents without CHD has a more similar profile to IE in adults.
- In children/adolescents without CHD, locations were similar to adults, including a predominance of left-sided IE.
- Acute heart failure was the most frequent complication, seen mainly in adults, and in children/adolescents without CHD.

### BACKGROUND

Infective endocarditis (IE) is a serious condition that carries high morbidity and mortality.<sup>1,2</sup> Recent changes in the epidemiology of IE are mainly related to population aging and the greater frequency of risk factors. These risk factors include cardiac surgeries, implantable cardiac devices (pacemakers and implantable cardioverter defibrillators), percutaneous treatment of structural heart diseases, and other healthcare-associated

procedures.<sup>3</sup> IE is uncommon in children,<sup>4</sup> although due to the progressive greater survival of children with congenital heart disease (CHD), its frequency is increasing.<sup>5–7</sup> Most previous studies that analyze the peculiarities of pediatric IE do not compare their clinical profile and evolution with adult IE.<sup>8–13</sup> In addition, there have been recent changes in the antibiotic prophylaxis recommendations for IE.<sup>14</sup> Children/adolescents and adults have differences in comorbidities and

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**Table 1.** Baseline demographic and clinical characteristics in patients with infective endocarditis according to age group.

	<18 years (N = 49)	≥18 years (N = 5541)	P
Variables (%)			
Age, median (IQR)	12 (2–16)	69 (58–77)	<0.001
Male sex	25 (51.0)	3739 (67.4)	0.02
Comorbidities			
Pulmonary disease	4 (8.1)	1043 (18.8)	0.057
Coronary artery disease	4 (8.1)	1498 (27.0)	0.003
Heart failure	14 (28.5)	1856 (33.5)	0.467
Diabetes	1 (2.0)	1624 (29.3)	<0.001
Human immunodeficiency virus	0	96 (1.7)	–
Intravenous drugs users	0	126 (2.2)	–
Peripheral arterial disease	3 (6.1)	598 (10.8)	0.293
Cerebrovascular disease	4 (8.1)	714 (12.8)	0.325
Cancer	1 (2.0)	895 (16.1)	0.007
Chronic kidney disease	4 (8.1)	1426 (25.7)	0.003
Liver disease	1 (2.0)	532 (9.6)	0.073
Congenital heart disease	31 (63.2)	310 (5.6)	<0.01
Native valve disease	28 (57.1)	2539 (45.8)	0.113
Age-adjusted Charlson Comorbidity Index, mean (SD)	0.7 (1.2)	5 (2.8)	<0.01

Data are shown as *n* (%) for categorical variables and median (interquartile rank) or mean (standard deviation) for continuous.

predisposing factors for IE that could lead to differences in etiology, diagnosis, and prognosis.

The aim of our work is to determine the clinical profile, risk factors, mode of presentation, and outcome of pediatric IE, and to compare it to adult IE. We have also analyzed IE in patients with and without CHD.

## METHODS

Prospective multicentre registry in 31 Spanish hospitals “Spanish Collaboration on Endocarditis—Grupo de Apoyo al Manejo de la Endocarditis infecciosa en ESpaña (GAMES)”.<sup>15–17</sup> All patients with a definite or possible diagnosis of IE were included from January 2008 to December 2020. Patients were classified into 2 groups according to the age at presentation: pediatric group with children and adolescents (<18 years) and adult group (≥18 years). Comparative analysis was performed between both groups. Patients were also compared according to the history of CHD.

This study was accomplished with the Declaration of Helsinki and was approved by the Ethics Committee of the recruiting hospitals. All patients provided written informed consent.

## Statistical analysis

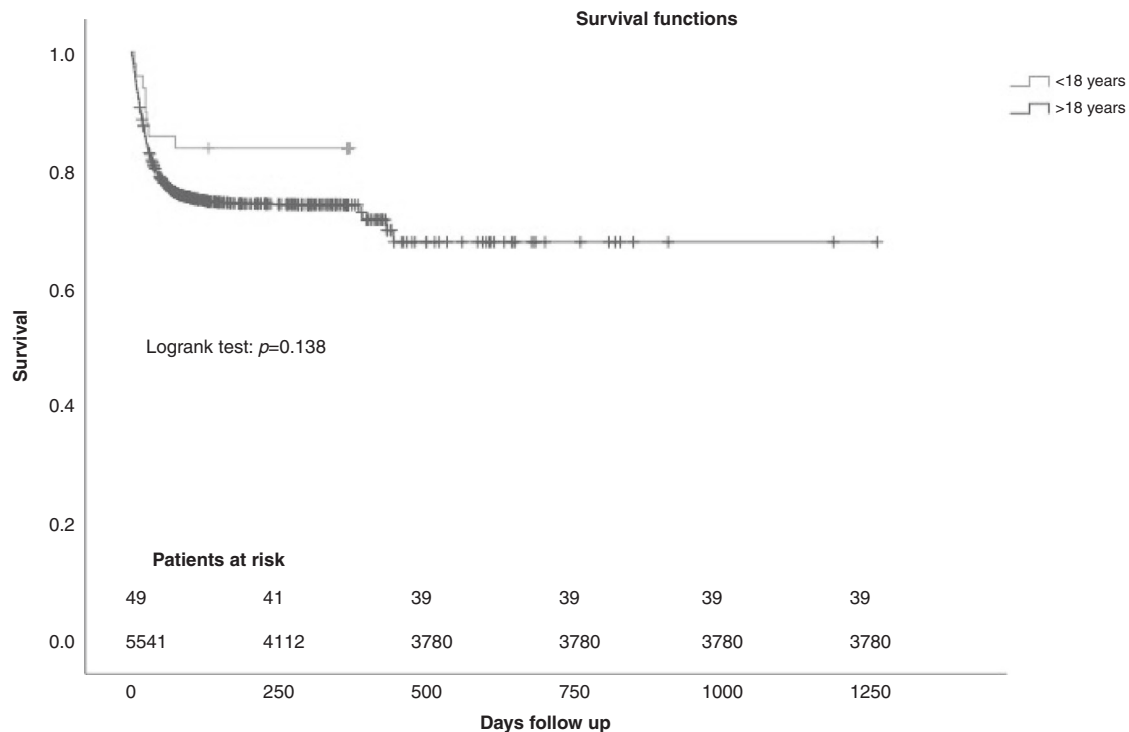
Continuous variables are shown as mean (standard deviation) or median (interquartile rank) for non-normally distributed variables. Categorical data are presented as frequencies and percentages. Continuous quantitative variables were compared using the Student's *t*-test and ANOVA for the comparison of means. Continuous variables

were compared using the Mann Whitney test and the Wilcoxon rank-sum in nonparametric data. Categorical variables were analyzed using the  $\chi^2$  test and the Fischer exact test. The goodness of fit of the final multivariate model was assessed again by the Hosmer–Lemeshow test. Multivariate analysis included multiple logistic regression techniques and Cox regression modeling for the study endpoints. To determine which variables were entered into the final model, we used a sequential inclusion and exclusion method, with an inclusion *P* threshold lower than 0.05 and exclusion over 0.1. The final model included age, sex, type of valve, comorbidities and previous medical history, complications, and history of CHD. Kaplan–Meier survival curve free of mortality at 1 year was generated

**Table 2.** Location, etiology, and clinical manifestations of infective endocarditis according to age group.

	<18 years (N = 49)	≥18 years (N = 5541)	P
Location			
Aortic	8 (16.3)	2882 (52.0)	<0.001
Mitral	11 (22.4)	2347 (42.4)	0.005
Tricuspid	7 (14.3)	287 (5.2)	0.013
Pulmonary	16 (32.7)	63 (1.1)	<0.001
Cardiac implanted electronic devices	1 (2.0)	561 (10.1)	0.057
Others	6 (12.2)	144 (2.6)	0.002
Poly-valvular involvement	1 (2.0)	796 (14.4)	0.007
Unknown	1 (2.0)	86 (1.6)	0.538
Native valve	28 (57.1)	3372 (60.9)	0.596
Prosthetic valve	12 (24.5)	1729 (31.2)	0.312
Conduits	9 (18.4)	646 (11.7)	0.146
Etiology			
<i>Staphylococcus aureus</i>	16 (32.7)	1233 (22.3)	0.082
Coagulase-negative <i>Staphylococci</i>	4 (8.2)	998 (18.0)	0.090
<i>Enterococcus</i>	3 (6.1)	784 (14.1)	0.146
<i>Streptococcus</i>	12 (24.5)	1415 (25.5)	0.867
<i>Candida</i>	1 (2.0)	87 (1.6)	0.542
No identifiable causative pathogen	1 (2.0)	456 (8.2)	0.125
Poly-microbial	1 (2.0)	85 (1.5)	0.534
Gram-negative bacilli	9 (18.4)	218 (3.9)	<0.001
Other microorganisms	2 (4.1)	227 (4.1)	0.897
Clinical manifestations			
Place of acquisition			
Community-acquired	29 (59.2)	3521 (63.5)	0.529
Nosocomial	14 (28.6)	1562 (28.2)	0.953
Health care-associated	6 (12.2)	458 (8.3)	0.315
Vegetation	38 (77.6)	4005 (72.3)	0.412
Intracardiac complications	12 (24.5)	1752 (31.6)	0.346
Perforation	6 (12.2)	778 (14.0)	0.719
Pseudoaneurysm	0	338 (6.1)	–
Abscess	6 (12.2)	916 (16.5)	0.421
Intracardiac fistula	1 (2.0)	139 (2.5)	0.835
Vascular phenomena	10 (20.4)	428 (7.7)	0.001
New murmur	23 (46.9)	1803 (32.5)	0.032
Heart failure	11 (22.4)	2242 (40.4)	0.010
Persistent bacteremia	10 (20.4)	596 (10.7)	0.030
Central nervous system involvement	6 (12.2)	1094 (19.7)	0.189
Embolism	14 (28.5)	1190 (21.4)	0.229
Acute renal failure	8 (16.3)	1987 (35.8)	0.004
Septic shock	7 (14.2)	687 (12.4)	0.690
Sepsis	20 (40.8)	912 (16.4)	<0.001
Surgical indication	29 (59.1)	3695 (66.6)	0.268
Cardiac surgery performed	22 (44.9)	2590 (46.7)	0.797
Indications for surgery (not performed)	7 (14.3)	1167 (21.1)	0.293
Inhospital deaths	8 (16.3)	1437 (25.9)	0.126
Deaths at 12 months	10 (20.4)	1761 (31.7)	0.088
Length of hospital stay, median (IQR)	38 (24–52)	35 (21–51)	0.568
Antibiotic therapy duration	42 (22–53)	38 (26–45)	0.308
Post-discharge sequelae (alive patients N 41/N 4104)	1 (2.4)	602 (14.6)	0.027

Data are shown as *n* (%) for categorical variables and median (interquartile rank) or mean (standard deviation) for continuous.



**Fig. 1** Survival in adults and children with infective endocarditis. Kaplan–Meier survival curves in adults and children with infective endocarditis.

with log-rank test analysis and considering censored episodes according to the time measured for each endpoint. All analyses were performed using SPSS for Windows, Version 26.0 (IBM, SPSS Statistics, Chicago, IL).

## RESULTS

### Demographic and comorbidities

During the study period, a total of 5590 patients with a diagnosis of IE were included in the GAMES registry. Forty-nine (0.9%) were <18 years, and 5541 (99.1%) were adults. Table 1 shows baseline, demographic, and clinical characteristics according to age group. Compared to the adult group, pediatric patients had a lower proportion of males, cardiovascular risk factors, and age-adjusted Charlson comorbidity index.

### Location and etiology

Right-sided location was common in the pediatric group and pulmonary valve location was present in one-third of children/adolescents. Left-sided location was common in adults with involvement of the aortic valve in 52% of those  $\geq 18$  years. Pacemaker/implantable cardioverter defibrillator-related and poly-valvular IE were uncommon in children/adolescents (only 1 case each) compared to adults (10% and 14%, respectively). Overall, the frequency of prosthetic valve IE was similar in adults and children/adolescents (31.2% and 24.5%, respectively).

The most common identified microorganism was *Staphylococcus aureus* (33% in the pediatric group and 22% in adults). Gram-negative etiology was more frequent in children/adolescents than in adults (33% vs. 4%).

### Complications, surgery, and outcome

Persistent bacteremia, sepsis, vascular phenomena, and new-onset murmurs were more common in the pediatric group than in the adult group (Table 2). We found a trend towards lower mortality in children compared to adults, which did not reach statistical significance in

**Table 3.** Multivariate analysis regarding in-hospital mortality.

	OR (95% CI)	P
Sex	12.58 (0.64–24.60)	0.095
Aortic IE	9.95 (0.62–15.93)	0.105
Coronary disease	0.77 (0.04–16.95)	0.867
Chronic kidney disease	1.34 (0.04–46.4)	0.873
Congenital valve disease	2.64 (0.21–34.03)	0.457
Vascular phenomena	6.65 (0.35–125.59)	0.206
Heart failure	32.40 (1.91–54.91)	0.016

Adjusted for age, previous medical history and baseline characteristics, location, and complications.

univariate analysis (Fig. 1) and in multivariate analysis (Table 3). Mortality risk was higher in patients who developed heart failure.

### IE with and without CHD

A total of 31 pediatric patients (63.3%) and 31 adults (5.6%) had a history of CHD (Table 4). In pediatric patients without CHD, left-sided IE was more common, and the most frequent location was the mitral valve (56%). In children/adolescents with CHD, right-sided IE was more common, and the most frequent location was the pulmonary valve (48%). Comorbidities tended to be more frequent in children/adolescents without CHD. In children with CHD, prosthetic IE was common (36% prosthetic valve + 26% repair material). Heart failure and valve perforation were more common in children/adolescents without CHD than in those with CHD. CHD was not associated with differences in mortality (odds ratio [OR] 2.64; 95% confidence interval [CI] 0.21–34.03,  $P = 0.457$ ). Figure 2 shows the most frequent types of CHD; Tetralogy of Fallot was present in 7 patients (23.3%).

**Table 4.** Baseline demographic and clinical characteristics in children/adolescents according to the history of congenital heart disease (CHD).

	No CHD (18)	CHD (31)	P
Variables (%)			
Age, median (IQR)	14 (1–15)	11 (3–16)	0.917
Sex (men)	12 (66.7)	13 (41.9)	0.095
Comorbidity			
Pulmonary disease	2 (11.1)	2 (6.4)	0.566
Coronary artery disease	3 (16.6)	1 (3.2)	0.098
Heart failure	3 (16.6)	11 (35.5)	0.202
Diabetes	1 (5.6)	0	—
Peripheral arterial disease	2 (11.1)	1 (3.2)	0.546
Cerebrovascular disease	2 (11.1)	2 (6.5)	0.618
Cancer	1 (5.6)	0	—
Chronic kidney disease	3 (16.6)	1 (3.2)	0.134
Liver disease	1 (5.6)	0	—
Native valvular disease	5 (27.8)	23 (74.2)	0.003
Age-adjusted Charlson comorbidity index mean (SD)	1 (1.7)	0.6 (0.8)	0.302
Location			
Aortic	4 (22.2)	4 (12.9)	0.443
Mitral	10 (55.6)	1 (3.2)	<0.001
Tricuspid	3 (16.7)	4 (12.9)	0.697
Pulmonary	1 (5.6)	15 (48.4)	0.004
Cardiac implanted electronic devices	0	1 (3.2)	—
Others	0	6 (19.4)	—
Poly-valvular involvement	0	1 (3.2)	—
Unknown	0	1 (3.2)	—
Native valve IE	16 (88.9)	12 (38.7)	0.001
Prosthetic valve IE	1 (5.6)	11 (35.5)	0.036
Conduits	1 (5.6)	8 (25.8)	0.127
Causative pathogens			
<i>Staphylococcus aureus</i>	7 (38.9)	9 (29.0)	0.537
Coagulase-negative <i>Staphylococci</i>	0	4 (12.9)	0.112
<i>Enterococcus</i>	2 (11.1)	1 (3.2)	0.267
<i>Streptococcus</i>	7 (38.9)	5 (16.1)	0.074
<i>Candida</i>	0	1 (3.2)	—
Other fungal species	0	0	—
No causative pathogens found	0	1 (3.2)	—
Anaerobics	0	0	—
Poly-microbial	0	1 (3.2)	—
Gram-negative bacilli	1 (5.6)	8 (25.8)	0.127
Other causative pathogens	1 (5.6)	1 (3.2)	0.605
Clinical course			
Place of acquisition			
Community-acquired	12 (16.7)	17 (54.8)	0.697
Nosocomial	4 (22.2)	10 (32.3)	0.453
Health care-associated	2 (11.1)	4 (12.9)	0.854

**Table 4.** continued

	No CHD (18)	CHD (31)	P
Vegetation	14 (77.8)	24 (77.4)	0.977
Intracardiac complications	6 (33.3)	6 (19.4)	0.316
Perforation	5 (27.8)	1 (3.2)	0.020
Pseudoaneurysm	0	0	—
Abscess	2 (11.1)	4 (12.9)	0.854
Intracardiac fistula	0	1 (3.2)	—
Vascular phenomena	5 (27.8)	5 (16.1)	0.465
New heart murmur	9 (50.0)	14 (45.1)	0.744
Heart failure	8 (44.4)	3 (9.6)	0.005
Persistent bacteremia	6 (33.3)	4 (12.9)	0.141
Central nervous system involvement	3 (16.7)	3 (9.7)	0.656
Embolization	6 (33.3)	8 (25.8)	0.574
Acute renal failure	4 (22.2)	4 (12.9)	0.395
Septic shock	4 (22.2)	3 (9.7)	0.398
Sepsis	7 (38.9)	13 (41.9)	0.834
Surgery indicated	9 (50.0)	20 (64.5)	0.319
Cardiac surgery performed	6 (33.3)	16 (51.6)	0.215
Cardiac surgery indicated but not performed	3 (16.7)	4 (12.9)	0.697
Inhospital mortality	4 (22.2)	4 (12.9)	0.443
Mortality at 12 months	5 (27.8)	5 (16.1)	0.329
Length of hospital stay, median (IQR)	40 (22–50)	43 (26–53)	0.876
Antibiotic therapy duration	42 (22–54)	38 (21–53)	0.928

Data are shown as *n* (%) for categorical variables and median (interquartile rank) or mean (standard deviation) for continuous.

The most common location in adults with CHD was the left valves, especially the aortic valve (63%) (Table 5 and Supplementary Table & Figure). Adults with CHD were younger and had less comorbidity than adults without CHD. Heart failure and valve perforation were also more common in adults without CHD than in those with CHD. Mortality was significantly higher in adults without CHD than in those with CHD (32.9% vs. 12.9%), and adults without CHD also underwent cardiac surgery less often than adults with CHD (46% vs. 61%).

## DISCUSSION

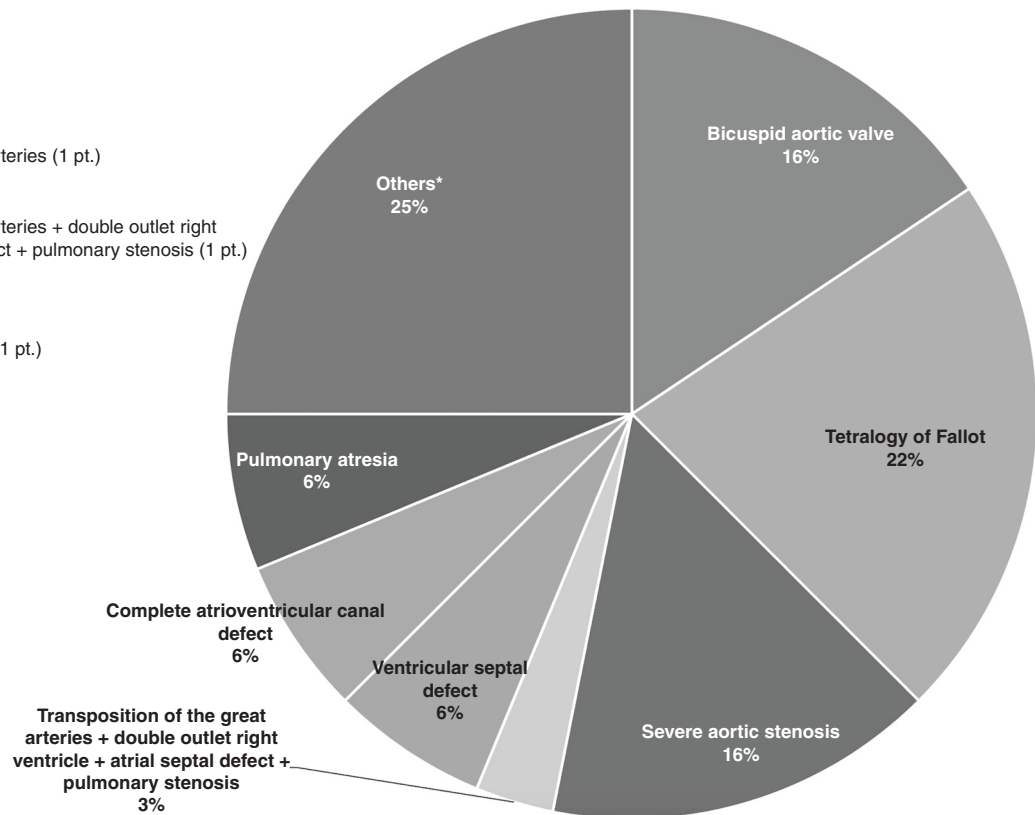
We have found substantial differences in the clinical profile and mode of presentation of pediatric IE compared to adult IE. This was particularly evident for children/adolescents with CHD.

IE in children is very rare and represents a minority of all cases.<sup>18–20</sup> About two-thirds of our pediatric patients had CHD, as previously reported.<sup>8,9,11,21–23</sup> In fact, CHD is the predominant underlying condition for pediatric IE in developed countries.<sup>4</sup> Most of our children/adolescents who did not have CHD presented other IE risk factors. The association of chronic conditions with non-CHD pediatric IE has also been found in previous studies.<sup>13,23</sup>

An increase in *Staphylococcus aureus* infections has been described,<sup>20</sup> especially in healthcare-related IE cases.<sup>24</sup> In children, both *Staphylococcus aureus* and *Streptococcus* spp. are frequent,<sup>9,12,13,21–23,25</sup> although in recent years there has been an

**\*Others**

- Single ventricle (1 pt.)
- Truncus arteriosus (1 pt.)
- Transposition of the great arteries (1 pt.)
- Patent foramen ovale (1 pt.)
- Transposition of the great arteries + double outlet right ventricle + atrial septal defect + pulmonary stenosis (1 pt.)
- Atrial septal defect (1 pt.)
- Pulmonary stenosis (1 pt.)
- Severe mitral regurgitation (1 pt.)



**Fig. 2 Types of congenital heart disease in the pediatric group.** Pie chart showing the frequency distribution of the most common types of congenital heart disease in the pediatric group.

increase in streptococcal infections.<sup>8</sup> We have found differences in the microbiological causative pathogens according to age and medical history. In children/adolescents, about 33% of cases of IE were caused by *Staphylococcus aureus*, while in adults this proportion was 22%. Furthermore, gram-negative bacilli were also common in children with CHD (25%). This high frequency of gram-negatives is noteworthy, since gram-negatives IE is rare, due to the difficulty of these microorganisms to adhere to the endothelium.<sup>26</sup> It should be noted that Gram-negative bacillary bacteremia is a common cause of bacteremia in the community.<sup>27</sup> Although some studies have estimated the rate of IE with negative cultures in 15–30% of cases,<sup>8,21</sup> in our registry only a minority of the total patients had negative blood cultures (<10%). An improvement in microbiological diagnostic techniques in the last decade may have facilitated the isolation of microorganisms that cause IE.<sup>28</sup>

The risk of IE can vary widely among CHD lesions, and the highest risk has been observed among patients with cyanotic CHD.<sup>13,29</sup> We have found that the most common CHD in children/adolescents with IE was the tetralogy of Fallot.<sup>13</sup> Right-sided IE was very common in our pediatric patients with CHD, as half of them presented with pulmonary valve involvement. Pulmonary valve IE is extremely rare in patients with a normal structural heart,<sup>30</sup> although its incidence is increasing in patients with complex CHD.<sup>11,31–34</sup>

Acute heart failure was the most frequent complication, seen mainly in adults, and children/adolescents without CHD. Heart failure is associated with mortality.<sup>35</sup> A greater left-sided valve involvement could be the cause of the higher frequency of heart failure in patients without CHD, since right valve involvement usually has better hemodynamics and prognosis.<sup>36</sup> Regarding treatment, more than half of our patients had an indication for surgical treatment, a proportion similar to that

reported in the study by Shamszad et al.<sup>25</sup> performed in patients <21 years.

The case fatality rate was similar in adults and children/adolescents. Pediatric patients presented a trend towards lower 12-month mortality but the rate of 20%, similar to that reported in a previous study<sup>21</sup> is still a high one. Previous data suggest a relation of severe CHD or complex cardiac interventions,<sup>37</sup> with higher mortality, but this was not the case in our cohort.

Compared to adults, we found that children/adolescents with IE and CHD have a different clinical profile and presentation. The differences with adults are probably more related to CHD itself than to age. It is foreseeable that the frequency of CHD-associated IE will rise in the near future<sup>5,20,37</sup> so, further studies focused on this group of patients would be welcome. Patients with cyanotic CHD should be closely monitored and adequate antimicrobial prophylaxis should be performed in them, as they are at the highest risk of IE.

Adults with CHD were younger and had fewer comorbidities than those without CHD, as previously described.<sup>38,39</sup> The most common etiology in adults with CHD was *Streptococci*, also described in previous reports.<sup>39,40</sup> The greater aortic valve involvement in adults with CHD and IE was related to the type of underlying heart disease, since in adults with CHD bicuspid aortic valve disease was present in almost half of cases and in children/adolescents, it was tetralogy of Fallot in near one out of four patients.

This study has some limitations. The number of pediatric patients was small, as some GAMES centers do not have pediatric departments, and Children Hospitals are not included in GAMES. The inclusion of patients in the registry took more than a decade, so it is possible that there were some changes in the management of patients according to the recommendations and changes in the clinical practice guidelines.<sup>14,41</sup>



**Table 5.** Baseline demographic and clinical characteristics in adults according to the history of congenital heart disease (CHD).

	No CHD (5231)	CHD (310)	P
Variables (%)			
Age, median (IQR)	70 (59–27)	43 (28–58)	<0.001
Sex (men)	3513 (67.1)	226 (72.9)	0.036
Comorbidity			
Pulmonary disease	1015 (19.4)	28 (9.0)	<0.01
Coronary artery disease	1429 (27.3)	69 (22.2)	0.051
Heart failure	1750 (33.4)	106 (34.2)	0.789
Diabetes	1586 (30.3)	38 (12.2)	<0.01
Peripheral arterial disease	585 (11.2)	13 (4.2)	<0.01
Cerebrovascular disease	690 (13.2)	24 (7.7)	0.005
Cancer	880 (16.8)	15 (4.8)	<0.01
Chronic kidney disease	1390 (26.6)	36 (11.6)	<0.01
Liver disease	518 (9.9)	14 (4.5)	<0.01
Native valvular disease	2331 (44.5)	208 (67.1)	<0.01
Age-adjusted Charlson comorbidity index mean (SD)	5 (3–7)	1 (0–3)	<0.01
Location			
Aortic	2685 (51.4)	197 (63.5)	<0.01
Mitral	2275 (43.5)	72 (23.2)	<0.01
Tricuspid	270 (5.2)	17 (5.5)	0.805
Pulmonary	35 (0.7)	28 (9.0)	<0.01
Cardiac implanted electronic devices	539 (10.3)	22 (7.1)	0.069
Others	122 (2.3)	22 (7.1)	<0.01
Poly-valvular involvement	743 (14.2)	53 (17.1)	0.158
Unknown	78 (1.5)	8 (2.5)	0.132
Native valve IE	3178 (60.8)	194 (62.6)	0.522
Prosthetic valve IE	1629 (31.1)	100 (32.3)	0.680
Conduits	612 (11.7)	34 (11.0)	0.696
Causative pathogens			
<i>Staphylococcus aureus</i>	1195 (22.8)	38 (12.3)	<0.01
Coagulase-negative <i>Staphylococci</i>	946 (18.1)	52 (16.8)	0.56
<i>Enterococcus</i>	764 (14.6)	20 (6.5)	<0.01
<i>Streptococcus</i>	1298 (24.8)	117 (37.7)	<0.01
<i>Candida</i>	84 (1.6)	3 (1.0)	0.38
Other fungal species	15 (0.3)	0	–
No causative pathogens found	432 (8.3)	24 (7.7)	0.748
Anaerobics	57 (1.1)	11 (3.5)	<0.01
Poly-microbial	80 (1.5)	5 (1.6)	0.907
Gram-negative bacilli	206 (3.9)	12 (3.9)	0.953
Other causative pathogens	121 (2.3)	23 (7.4)	<0.01
Clinical course			
Place of acquisition			
Community-acquired	3291 (62.9)	230 (74.2)	<0.01
Nosocomial	1503 (28.7)	59 (19.0)	<0.01
Health care-associated	437 (8.4)	21 (6.8)	0.326

**Table 5.** continued

	No CHD (5231)	CHD (310)	P
Vegetation	3794 (72.5)	211 (68.1)	0.088
Intracardiac complications	1639 (31.3)	113 (36.5)	0.126
Perforation	734 (14.0)	44 (14.2)	0.936
Pseudoaneurysm	308 (5.8)	30 (9.6)	0.007
Abscess	849 (16.2)	67 (21.6)	0.013
Intracardiac fistula	125 (2.4)	14 (4.5)	0.020
Vascular phenomena	396 (7.5)	32 (10.3)	0.078
New heart murmur	1675 (32.0)	128 (41.3)	0.001
Heart failure	2153 (41.1)	89 (28.7)	<0.01
Persistent bacteremia	572 (10.9)	24 (7.7)	0.078
Central nervous system involvement	1048 (20.0)	46 (14.8)	0.026
Embolization	1128 (21.5)	62 (20.0)	0.515
Acute renal failure	1934 (36.9)	53 (17.1)	<0.01
Septic shock	661 (12.6)	26 (8.3)	0.027
Sepsis	872 (16.6)	40 (12.9)	0.082
Surgery indicated	3479 (66.5)	216 (69.7)	0.425
Cardiac surgery performed	2401 (45.9)	189 (61.0)	<0.01
Cardiac surgery indicated but not performed	1136 (21.7)	31 (10.0)	<0.01
Inhospital mortality	1406 (26.9)	31 (10.0)	<0.01
Mortality at 12 months	1721 (32.9)	40 (12.9)	<0.01
Length of hospital stay, median (IQR)	35 (21–51)	32 (20–50)	0.052
Antibiotic therapy duration	38 (20–45)	38 (28–48)	0.254

Data are shown as *n* (%) for categorical variables and median (interquartile rank) or mean (standard deviation) for continuous.

In conclusion, most IE cases in children and adolescents are seen in patients with CHD that have a more common right-sided location and a lower prevalence of heart failure compared with those without CHD. Pediatric IE without CHD has a similar profile to IE in adults.

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## AUTHOR CONTRIBUTIONS

L.V., M.A.G., P.M., M.M.-A., M.V., M.C.F., M.C.-B., A.d.A., M.Á.R.-E., J.M.M., A.J.G.-A., D.d.C.C., E.G.-V., and M.M.-S. contributed to the design and implementation of the research, to the analysis of the results, and to the writing of the manuscript.

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## COMPETING INTERESTS

The authors declare no competing interests.

## CONSENT STATEMENT

All patients provided written informed consent.

## ADDITIONAL INFORMATION

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