Infective Endocarditis in the Pediatric Patient: A 60-Year Single-Institution Review

Jennifer A. Johnson, DO; Thomas G. Boyce, MD; Frank Cetta, MD; James M. Steckelberg, MD; and Jonathan N. Johnson, MD

Abstract

Objective: To determine the epidemiology of infective endocarditis (IE) presenting in pediatric patients during a 60-year period at our institution.

Patients and Methods: In this retrospective medical record review, we extracted demographic characteristics, diagnostic variables, and outcomes for patients less than 20 years of age diagnosed with IE from January 1, 1980, to June 30, 2011. We compared this cohort with a previously reported cohort of pediatric patients with IE from our institution diagnosed from 1950 to 1979.

Results: We identified 47 patients (24 males; mean $\pm$ SD age at diagnosis, 12.3 ± 5.5 years [range, 1 day to 18.9 years]) who had 53 episodes of IE. The most common isolated organisms were viridans streptococci (17 of 53 episodes [32%]) and *Staphylococcus aureus* (12 of 53 episodes [23%]). Of the 47 patients, 36 (77%) had congenital heart disease, 24 of whom had cardiac surgery before their first episode of IE (mean $\pm$ SD time to IE diagnosis after surgery, 4.2 ± 3.2 years [range, 64 days to 11.3 years]). Fourteen patients (30%) required valve replacement because of valvular IE, and 16 (34%) had complications, including mycotic aneurysm, myocardial abscess, or emboli. Vegetations were identified using echocardiography in 37 of the 53 unique episodes of IE (70%). Endocarditis-related mortality occurred in 1 patient. Compared with the historical (1950-1979) cohort, there were no differences in patient demographic characteristics, history of congenital heart disease, or infecting organisms. One-year mortality was significantly lower in the modern cohort (4%) compared with the historical cohort (38%) ($P < .001$).

Conclusion: Most pediatric episodes of IE occur in patients with congenital heart disease. Mortality due to endocarditis has decreased in the modern era.

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Infective endocarditis (IE) is rare in the pediatric population and historically carries a high risk for morbidity and mortality. The incidence of pediatric IE is thought to be increasing in the current era.¹ Compared with adults, the incidence of IE in pediatric patients is much lower, occurring at a rate of 0.34 to 0.64 cases per 100,000 per year.² In developed countries, there has been a decline in rheumatic fever; however, there has been increased survival of patients with congenital heart disease (CHD). This increase in the overall number of patients with CHD may be a major component of the increased incidence of IE.^{2,3} Advancements in cardiac surgery for congenital defects include the increased use of bioprosthetic and synthetic materials that may further increase the risk for development of IE in patients with CHD.⁴

Advances in echocardiography since the 1980s have allowed for improved anatomic delineation of vegetations in patients with IE and have helped in decisions between medical or surgical intervention. Finally, antibiotic prophylaxis for high-risk patients has been recommended by the American Heart Association since 1955.⁵ The use of antibiotic prophylaxis is thought to reduce the incidence of IE in high-risk patients after dental and genitourinary procedures.⁵

Our institution is a referral center for the care of infants and children with CHD. A previous study of pediatric IE published in 1982 examined cases seen at Mayo Clinic between 1950 and 1979.⁶ In the current study, we reviewed our experience in the treatment of pediatric IE between 1980 and 2011 and compared differences in patient characteristics and outcomes between the 2 studies. We further sought to assess the impact of echocardiography, surgical treatment, and antibiotic prophylaxis on the current cohort.

PATIENTS AND METHODS

In this institutional review board–approved study, we searched the Mayo Clinic Division of Infectious Diseases endocarditis database for any patient younger than 20 years diagnosed with IE between January 1, 1980, and June 30, 2011. We reviewed all potential cases to confirm that they met the modified Duke criteria for the diagnosis of IE.⁷ Extracted variables included patient demographic characteristics, infecting organism, history of CHD, prior cardiac surgery, morbidity, mortality, previous dental procedures, and the diagnostic imaging utilized. When available, all diagnostic imaging studies were

From the Division of Pediatric Cardiology (J.A.J., F.C., J.N.J.), Division of Pediatric Infectious Diseases (T.G.B.), Division of Cardiovascular Diseases (F.C.), and Division of Infectious Diseases (J.M.S.), Mayo Clinic, Rochester, MN.

reviewed by the authors to confirm diagnostic and testing outcomes. We defined morbidity as any diagnosis of mycotic aneurysm, septic emboli, stroke, or abscess at the time of IE.

The data from our review were compared with the previously reported cohort from our institution (1950-1979).⁶ The historical (1950-1979) cohort was designated as cohort 1, and the current era (1980-2011) cohort was designated as cohort 2. Of note, in the cohort 1 study, the investigators did not report mean age and age range but did report the number of patients in specific age groups (<1, 1-3, 4-6, 7-9, 10-12, and 13-15 years). Patients between the ages of 16 and 19 were not included in cohort 1.

STATISTICAL ANALYSES

Data were analyzed using JMP 7.0 statistical software (SAS Institute Inc, Cary, NC). All continuous variables were reported as mean $\pm$ SD. Proportions were analyzed and compared using the Fisher exact test. Means were analyzed using the independent group *t* test for means. A 2-sided *P* value of less than .05 was considered statistically significant.

RESULTS

Demographic Characteristics and Cardiac History

During the 60-year study period (1950-2011) encompassing the 2 cohorts, 97 pediatric patients with IE were seen at our institution. These 97 patients were diagnosed with a total of 103 unique cases of IE. Patient demographic characteristics for both cohorts are shown in Table 1. There were no statistically significant differences for gender, age, and history of CHD. The most common time of presentation in both cohorts was in the teenage years. In cohort 1, 20 of 50 diagnosed episodes IE (40%) occurred in patients between 13 and 15 years of age. In cohort 2, 19 of 53 diagnosed episodes of IE (36%) occurred in patients aged 16 to 19 years, and an additional 10 episodes (19%) occurred in patients aged 13 to 15 years.

The different types of CHD found in each cohort are shown in Table 2. Ventricular septal defects (VSDs) were the predominant CHD in cohort 1 (13 of 37 patients [35%]), while in cohort 2, only 3 of 40 episodes of IE (8%) occurred in patients with an

TABLE 1. Baseline Demographic Characteristics of 2 Infective Endocarditis Cohorts^{a,b}

Characteristic	Cohort 1 (1950-1979) (N=50)	Cohort 2 (1980-2011) (N=47)	
	All IE episodes (N=50)	First IE episode for each patient (N=47)	All IE episodes (N=53) ^c
Male	34 (68)	24 (51)	26 (49)
Age (y)			
Mean	NA	12.1	12.3
Range	NA	0.01-18.9	0.01-18.9
Cases (No.) per age group (y)			
<1	5	4	4
1-3	2	3	3
4-6	8	2	2
7-9	7	5	6
10-12	8	7	9
13-15	20	9	10
16-19	NA	17	19
Rheumatic heart disease	4 (8)	0	0
Congenital heart disease	37 (74)	36 (77)	40 (75)
Prior cardiac surgery	17 (34)	26 (55)	27 (51)
Mean interval from IE to previous surgery (y)	NA	4.2	4.2
IE $\leq$ 3 mo postoperatively	8 (47)	2 (8)	2 (7)
IE >3 mo postoperatively	9 (53)	24 (92)	25 (93)

^aIE = infective endocarditis; NA = not available.

^bData are presented as No. (percentage) and mean $\pm$ SD unless indicated otherwise.

^cIn cohort 2, 6 patients had multiple episodes of IE, all of whom had 2 distinct episodes.

TABLE 2. Congenital Heart Disease Lesions in 2 Cohorts of Infective Endocarditis^a

Lesion	Cohort 1 (1950-1979) (N=50)	Cohort 2 (1980-2011) (N=47)	
	All IE episodes (n=37)	First IE episode for each patient (n=36)	All IE episodes (n=40) ^b
Aortic/subaortic disease	7	7	9
Coarctation	3	3	3
Complete AVSD	0	2	2
Complete TGA	2	1	1
Congenitally corrected TGA	0	3	3
Double-inlet left ventricle	0	1	1
Mitral valve prolapse	0	4	4
Patent ductus arteriosus	2	0	0
Pulmonary atresia with VSD	0	7	8
Pulmonary valve stenosis	1	0	0
Tetralogy of Fallot	6	2	2
Truncus arteriosus	1	4	4
Ventricular septal defect	13	2	3
Other complex lesions	2	0	0
Total	37	36	40

^aAVSD = atrioventricular septal defect; IE = infective endocarditis; TGA = transposition of the great arteries; VSD = ventricular septal defect.

^bIn cohort 2, 4 patients had multiple episodes of IE.

isolated VSD ($P<.001$). Conversely, pulmonary atresia with VSD was more common in cohort 2 (7 of 36 patients [19%]) than in cohort 1 (0 of 37 patients).

The number of patients with IE who had normal intracardiac anatomy was similar between cohort 1 (13 of 50 [26%]) and cohort 2 (11 of 47 [23%]). In cohort 2, this included patients with a nosocomial infection ($N=1$), intravenous drug use ($N=1$), and postpartum IE ($N=1$). The remainder of patients with normal intracardiac anatomy presented with prolonged fever. There were 4 patients in cohort 1 with a history of rheumatic heart disease, compared with none in cohort 2.

Prior Cardiac Surgery

During the 60-year study period, 43 patients had 44 cardiovascular operations before IE diagnosis (Table 1). In cohort 1, 17 patients had operations before IE diagnosis, 8 (47%) of whom were diagnosed with IE within 3 months postoperatively. All 17 of these patients had CHD. In cohort 2, 26 patients were diagnosed with 27 cases of IE occurring after an operation (Figure 1). Only 2 of these 27 IE cases (7%) were diagnosed within 3 months of surgery ($P<.007$ compared to cohort 1). Of 26 patients in cohort 2 with cardiovascular surgery before IE

diagnosis, 24 (92%) had CHD. Two patients with normal cardiac anatomy had prior cardiac operations; one valve replacement in a patient with a prior episode of IE and one valve repair secondary to trauma. The mean $\pm$ SD time between the last operation and the subsequent IE diagnosis was 4.2 ± 3.2 years (range, 64 days to 11.3 years). Unoperated patients with IE in cohort 2 who had CHD included 3 with VSDs, 3 with mitral valve prolapse, 2 with congenitally corrected transposition of the great arteries, 1 with tetralogy of Fallot, 1 with coarctation of the aorta, and 2 with aortic valve disease. One patient with a subaortic membrane had 2 episodes of IE, one before surgical resection of the subaortic membrane and another episode 7 years later.

In cohort 2, 17 of the 47 patients (36%) had prosthetic valves at the time of diagnosis of IE. Sixteen of these patients had CHD, and 1 patient had a previous IE infection requiring a mitral valve replacement. The most commonly infected valve was the pulmonary valve, with 3 bioprosthetic valves and 5 homografts infected. Other valve infections included 7 patients with prosthetic aortic valves and 2 patients with prosthetic mitral valves. The mean $\pm$ SD time between valve replacement and subsequent IE diagnosis was 4.6 ± 4.5 years (range, 66 days to 18.1 years).

Pathogens

Blood culture results were positive in 47 of 53 IE cases (89%) in cohort 2. The causative organisms in each cohort are shown in Table 3. Viridans streptococci and *Staphylococcus aureus* were the most common pathogens in both cohorts. In the 12 cases of *S aureus* infection in cohort 2, none were found to be methicillin resistant. In cohort 1, methicillin resistance was not identified. There were several unique bacterial isolates found in cohort 2 patients, including *Mycobacterium wolinskyi*, *Streptococcus pyogenes*, and *Streptococcus agalactiae*.

Morbidity and Mortality

The percentage of patients with morbidity due to mycotic aneurysm, septic emboli, stroke, or abscess was similar between cohort 1 (16 of 50 patients [32%]) and cohort 2 (16 of 47 patients [34%]) (Figure 2). *S aureus* infections were related to morbidity in 5 of 16 patients (31%) in cohort 2.

The overall 1-year mortality was lower in cohort 2 (2 of 47 patients [4%]) compared with cohort 1 (19 of 50 patients [38%]; $P < .001$). Further, mortality in patients without CHD was lower in cohort 2 (1 of 11 patients [9%]) compared with cohort 1 (4 of 19 patients [21%]). In cohort 2, only 1 patient died during the initial admission for IE. One patient died during surgery for elective valve replacement 6 months after IE diagnosis. There were 3 other deaths in cohort 2 on late follow-up, all occurring at least 5 years after infection; 1 death occurred after surgical complications from elective valve replacement, and 2 occurred due to multiorgan failure. All 5 deaths in cohort 2 occurred more than 3 months after a cardiac operation (range, 0.6–23.4 years). In cohort 1, *S aureus* infections were involved in 9 of the 19 fatal

cases (47%), compared with none of the fatal cases in cohort 2.

Treatment

Of the 53 cases of IE in cohort 2, 49 (92%) had antibiotic treatment plans available for our review. The typical intravenous antimicrobial treatment course was 4 to 6 weeks. In cohort 2, surgical intervention was performed in 16 of 47 patients (34%), resulting in 17 surgical procedures (1 patient needed a second valve replacement after a recurrent episode of IE). Of these 16 patients, 14 required valve replacement and 2 had vegetation removal only. There was no surgical mortality. Data were unavailable for cohort 1 regarding surgical interventions for endocarditis.

Echocardiography

In cohort 2, transthoracic and transesophageal echocardiography were used to detect 37 vegetations in 53 cases (70%) of IE. Transthoracic echocardiography identified vegetations in 33 cases (62%), while an additional 4 patients (8%) had vegetations found by transesophageal echocardiography only. There was little difference between the rate of echocardiographic detection of vegetations in cases with (27 of 39 [69%]) vs without (10 of 14 [71%]) CHD. Echocardiography was not utilized in cohort 1.

Prophylaxis

In cohort 2, 5 patients with CHD had undergone dental procedures less than 2 weeks before IE diagnosis, 4 (80%) of whom had received appropriate antibiotic prophylaxis before the procedure. In the

TABLE 3. Pathogenic Etiology in 2 Cohorts of Infective Endocarditis

Organism	Cohort 1 (1950-1979) (N=50)	Cohort 2 (1980-2011) (N=53) ^a
Congenital heart disease	37	40
Viridans streptococci	11	14
<i>Staphylococcus aureus</i>	12	9
<i>Pseudomonas aeruginosa</i>	3	0
<i>Staphylococcus epidermidis</i>	1	1
<i>Haemophilus influenzae</i>	1	3
Nutritionally variant streptococci	0	3
<i>Streptococcus pyogenes</i>	0	1
<i>Escherichia coli</i>	1	0
<i>Streptococcus pneumoniae</i>	1	1
<i>Mycobacterium wolinskyi</i>	0	1
<i>Enterococcus faecalis</i>	0	1
<i>Candida parapsilosis</i>	0	1
<i>Candida albicans</i>	1	0
Negative blood culture result	4	5
No culture done	2	0
Rheumatic heart disease	4	0
Viridans streptococci	3	0
<i>S aureus</i>	1	0
No cardiac disease	9	13
Viridans streptococci	0	3
<i>S aureus</i>	6	3
<i>S epidermidis</i>	2	2
<i>Streptococcus agalactiae</i>	0	1
<i>Cardiobacterium hominis</i>	1	0
<i>Neisseria meningitidis</i>	0	1
<i>Haemophilus parainfluenzae</i>	0	1
<i>S pneumoniae</i>	0	1
Negative blood culture result	0	1

^aIn cohort 2, there were 53 episodes of infective endocarditis in 47 patients.

1 patient who did not receive antibiotic prophylaxis, the presence of congenital heart disease was unknown at the time of the dental visit.

DISCUSSION

Infective endocarditis is rare in the pediatric population but can cause significant morbidity and mortality, particularly in patients with CHD. We report a comprehensive review of IE cases seen at our institution during a 60-year period.

Demographic Characteristics and Epidemiology

The demographic characteristics of our 2 cohorts were similar with respect to gender, frequency of CHD, and predominance of IE patients in the teen-

aged population. Previous studies have demonstrated a bimodal age distribution of IE in infancy and late teenage years.¹ Although our data confirm the prominence of IE diagnosis in the late teenage years, this finding may be a function of the relatively small number of young children in our cohort. Rheumatic heart disease was thought to be associated with IE in 30% to 50% of patients in early case series.¹ During the past 60 years at our institution, IE in patients with rheumatic heart disease has essentially disappeared. This trend in rheumatic heart disease has been shown in several other case series.^{4,8-11}

A major risk factor for IE in patients with CHD is prior surgical intervention. In our study, there was a history of cardiovascular surgery in 34% of pa-

FIGURE 2. Single-slice computed tomographic image from a 5-month-old patient with complex congenital heart disease and enterococcal endocarditis. Note the 2 large mycotic aneurysms (*) emerging from the descending aorta and proximal left iliac artery.

tients in cohort 1 and 55% of patients in cohort 2. The larger percentage of patients with prior surgery in cohort 2 is likely due to improved long-term survival of patients with complex CHD and the routine use of synthetic material and valve prostheses. Early postoperative (≤ 3 months) IE was significantly lower in cohort 2 ($P < .007$), probably due to many factors including the routine use of intraoperative antibiotic regimens and improved sterile technique. An interesting finding was that cohort 2 patients with CHD who experienced IE had more complex lesions than those in cohort 1. The frequency of simple isolated VSD was higher in the early cohort and relatively rare in the modern group (Table 2).

Advances in surgical techniques and postoperative care have improved the life span of many patients with CHD, and subsequently more surgical interventions are performed in the modern era. In cohort 2, patients more commonly had complex cardiac anatomy. Pulmonary atresia was the most common diagnosis in cohort 2 (7 of 36 patients [19%]), while an isolated VSD was most common in cohort 1 (13 of 37 patients [35%]). It can be speculated that improvements in early detection of CHD with echocardiography and improved surgical techniques have facilitated performance of definitive procedures earlier in life, thus decreasing the risk of IE infection due to unrepaired CHD. Our institution has been a referral center for pulmonary atresia in recent years, and this could contribute to the high frequency of patients with pulmonary atresia in cohort 2.

Pathogens

In each cohort, viridans streptococci and *S aureus* comprised more than half of the cases of IE. This finding is similar to those in other published series.^{1,4,9-11} In our study, there was only 1 case of *Enterococcus faecalis* endocarditis (2%), compared with 7% to 16% reported in other series.^{4,9,11} This may be due to the relatively few infants in our study, since *E faecalis* infection has been shown to be more common in infantile endocarditis.⁹

Relatively rare bacteria were found in some of our recent IE cases. β -Hemolytic streptococci seldom cause IE in the current era but were identified in 1 postpartum patient with *S agalactiae* as well as 1 CHD patient with *S pyogenes*. *S agalactiae* IE has been reported as a rare cause of postpartum IE with a high rate of morbidity and mortality.¹² *S pyogenes* is thought to cause less than 5% of cases of endocarditis, has been linked to intravenous drug use or previous varicella infection, and usually affects the right side of the heart.¹³ *M wolinskyi* was isolated from one of our CHD patients. This gram-positive, nonmotile, acid-fast rod is a rare pathogen, sometimes seen in patients with a history of trauma and osteomyelitis or cellulitis.¹⁴

Morbidity and Mortality

Historically, IE has a high risk of morbidity and mortality, with reports of mortality ranging from 4% to 24%.^{1,4,9-11} In both of our cohorts, approximately 80% of patient deaths (15 of 19 patients in cohort 1, 4 of 5 patients in cohort 2) occurred in patients with CHD. The overall 1-year mortality was significantly ($P < .001$) lower in the modern era (4%) compared with the historical era (38%). Of the 5 patients in cohort 2 who died, 4 had CHD, but in only 1 was IE the primary cause of death. One patient died 6 months after IE diagnosis during elective valve replacement. The other 3 died at least 5 years after the acute episode of IE from multiple causes. All 5 deaths occurred in patients with previous cardiac operations, and all occurred more than 3 months postoperatively.

S aureus IE has been reported to be associated with a poor prognosis.^{1,9,11} This association was confirmed in our study because *S aureus* was involved in 9 of 19 deaths in cohort 1. Although it was not diagnosed in any of the 5 deaths in cohort 2, it was involved in 5 of 16 patients (31%) who had significant morbidity. Morbidity from secondary complications such as septic emboli, mycotic aneurysms, and abscesses is common in patients with IE. In both cohorts in our study, these secondary complications occurred in more than 30% of cases.

Echocardiography

The routine use of 2-dimensional echocardiography, starting in the 1980s, has increased the capacity to diagnosis IE. Echocardiographic features such as vegetations, abscesses, prosthetic valve partial dehiscence, and new valvular regurgitation are all defined as major criteria in the modified Duke criteria.⁷ The sensitivity of echocardiography ranges from 51% to 67% in different case series.^{8-10,15} In our study, the percentage of vegetations identified by echocardiography was 70%, with the majority involving the mitral and aortic valves in patients with CHD. Transesophageal echocardiography identified vegetations in 4 patients in whom transthoracic echocardiography had not detected a vegetation. Previous case series have shown improved sensitivity in vegetation identification by echocardiography in patients with normal cardiac anatomy as opposed to those with complex CHD.^{8,11} In our study, vegetations in patients with CHD and normal cardiac anatomy were identified by echocardiography at a similar rate (69% and 71%, respectively).

Prophylaxis

In 2007, the American Heart Association revised the guidelines for antibiotic prophylaxis in patients with CHD. The guidelines were changed because of the lack of evidence that prophylactic antibiotic administration prevented IE due to an invasive procedure in low-risk patients.⁵ In our study, we found 5 patients with CHD who had known dental procedures less than 2 weeks before IE diagnosis. All but 1 patient took antibiotics before the procedure. This finding demonstrates that antibiotic prophylaxis may not always be effective, even when administered appropriately.

CONCLUSION

Infective endocarditis continues to be rare in the pediatric population, and most cases now occur in patients with complex CHD rather than the isolated VSD that predominated earlier cohorts. Mortality related to endocarditis is significantly lower in the modern era. The most commonly diagnosed pathogens in pediatric IE have remained consistent throughout the 60 years of our study. Unusual pathogens are now more common in patients with CHD. Modern echocardiographic techniques facilitate the diagnosis of IE by providing identification of IE in patients with normal cardiac anatomy and in those with complex CHD.

Abbreviations and Acronyms: CHD = congenital heart disease; IE = infective endocarditis; VSD = ventricular septal defect

Correspondence: Address to Jonathan N. Johnson, MD, Division of Pediatric Cardiology, Mayo Clinic, 200 First St SW, Rochester, MN 55905 (johnson.jonathan@mayo.edu).

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