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The Changing Epidemiology of Pediatric Endocarditis at a Children's Hospital Over Seven Decades

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Abstract

This study sought to determine whether improvements in the care of children with congenital heart disease (CHD) have changed the epidemiology of infective endocarditis (IE). A retrospective study of patients 18 years of age and younger treated for IE from 1992 to 2004 (era 3) was conducted at the authors' children's hospital in New York City. This study was compared with two previous studies conducted at the same hospital from 1930 to 1959 (era 1) and from 1977 to 1992 (era 2). During the three eras, IE was diagnosed for 205 children with a median age of 8 years during eras 1 and 2, which decreased to 1.5 years during era 3, partly because of IE after cardiac surgery for young infants. In era 3, nonstreptococcal and nonstaphylococcal pathogens associated with hospital-acquired IE increased. Complications from IE declined during era 3, but after the widespread availability of antibiotics in 1944, crude mortality rates were similar in eras 1 (32%), 2 (21%), and 3 (24%). However, in era 3, mortality occurred only among subjects with hospital-acquired IE. The epidemiology of pediatric IE has changed in the modern era. Currently, IE is

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Conflicts of interest statement

The authors have no conflicts of interest to disclose.

most likely to occur among young children with complex congenital heart disease. Pediatric IE remains associated with high crude mortality rates when it is acquired in the hospital.

Keywords

Congenital heart disease; Endocarditis; Pediatrics

Infective endocarditis (IE) in children is relatively rare but causes significant morbidity and mortality when it occurs. Several case series have demonstrated that the epidemiology of pediatric IE has changed in parallel with advances in medical care [1,2,12,15,20,25,34]. As the incidence of rheumatic fever has declined in developed countries due to reduction in overcrowded living conditions and improvements in diagnosis and care of pharyngitis caused by group A streptococci [26,28], the importance of rheumatic heart disease as an underlying risk factor for pediatric IE has substantially decreased. Surgical advances for children with congenital heart disease (CHD), including the introduction of bioprosthetic or synthetic materials, have improved the outcomes and life expectancy of such children, thereby increasing the number of children at risk for IE [2,9,18].

The increased use of central venous catheters (CVCs) among hospitalized children, including premature infants, also has expanded the pediatric population at risk for IE [18]. Finally, the escalating complexity of hospitalized patients coupled with the use of broad-spectrum antibiotics has led to the emergence of multidrug-resistant organisms causing hospital-acquired endocarditis [17,18].

Our children's hospital serves as a referral center for infants and children with CHD. Two previous case series have described the epidemiology of pediatric IE at our institution from 1930 to 1959 (era 1) and from 1977 to February 1992 (era 2) [3,31].

The current study reviewed the demographic and clinical characteristics of patients who received a diagnosis of IE from March 1992 to December 2004 (era 3) to explore changes in the epidemiology of pediatric IE. We hypothesized that the risk factors for IE had changed during era 3 due to management of increasingly complex CHD lesions in younger children. We further hypothesized that the types of pathogens had changed and included more multidrug-resistant organisms.

Materials and Methods

Study Design

The electronic medical records of children 18 years of age and younger admitted to the Morgan Stanley Children's Hospital of New York-Presbyterian, Columbia University Medical Center either treated for IE or with a diagnosis of IE at autopsy from 1 March 1992 to 31 December 2004 were reviewed retrospectively. Potential study subjects were identified from discharge International Classification of Diseases-9 (ICD-9) codes for endocarditis, echocardiogram reports, consult records of the Division of Pediatric Infectious Diseases, and autopsy reports, as previously described [31]. The Institutional Review Board at Columbia University Medical Center approved the performance of this study with a waiver of informed consent documentation.

Case Definitions

The same case definitions were used in eras 2 and 3 to facilitate comparisons. These included one of the following four definitions [31]:

1. Treatment for IE plus either positive blood culture and a vegetation demonstrated on echocardiogram or positive blood culture, signs, and symptoms consistent with IE (e.g., fever, fatigue), supporting laboratory data (e.g., elevated erythrocyte sedimentation rate, positive ventilation perfusion scan), or physical findings (new or changing murmur, hepatomegaly, embolic phenomenon)
2. Positive blood culture, CHD, and fever with no other apparent source of fever
3. Negative blood culture, fever, and vegetation on echocardiogram or embolic phenomena
4. IE diagnosed at autopsy.

In era 3, the underlying heart conditions of the subjects were further characterized by hemodynamic status (acyanotic vs cyanotic) at the time of the diagnosis of IE, by the need for antibiotic prophylaxis for IE as currently recommended [37], and by the level of risk for IE (high, moderate, negligible) [10]. Examples of high-risk lesions for IE are prosthetic heart valves, a history of IE, complex cyanotic congenital heart disease, and surgically constructed systemic pulmonary shunts or conduits [10]. Examples of moderaterisk lesions for IE include uncorrected patent ductus arteriosus (PDA), uncorrected ventricular septal defect (VSD), coarctation of the aorta, and acquired valvar dysfunction due to rheumatic heart disease or collagen vascular disease and hypertrophic cardiomyopathy [10]. Negligible risk conditions for IE include secundum atrial septal defects.

Study subjects were considered premature if their gestational age was less than 37 weeks. Early postoperative IE was defined as occurring within 2 months after cardiac surgery [16,31]. Hospital-acquired IE developed 48 h or more after admission [17]. Infective endocarditis was defined as polymicrobial if two pathogens were isolated from either the same blood culture or separate blood cultures during the same period. Coagulase-negative staphylococci (CoNS) were considered pathogens if two or more blood cultures tested positive for these microorganisms. Recurrence of IE was diagnosed if a second episode of IE occurred after treatment of an initial IE episode [7].

Data Collection and Analysis

The electronic medical records of potential subjects were reviewed by four physicians with expertise in pediatric cardiology and infectious diseases. A standardized data collection instrument was developed in Microsoft Access (Microsoft Corporation, Redmond, WA, USA). Demographic and clinical characteristics, cardiac lesions, blood culture results, echocardiographic findings, CVC use, outcomes, and pathology reports were abstracted.

The findings of this study were compared with those of the two previous reports from our children's hospital [3,31]. When appropriate, chi-square tests and analysis of variance (ANOVA) tests were performed using the SAS 9.1.3 (SAS Institute, Cary, NC, USA) statistical software program.

Results

Demographic and Clinical Characteristics

The demographic and clinical characteristics of the pediatric subjects with IE from the three eras are displayed in Table 1. The proportion of males with IE increased over time ($P = 0.004$). The median age at diagnosis was 8 years during the first two eras but decreased to the age of 1.5 years during era 3. The younger age of the children in era 3 was partly due to infants with IE (median age, 7.4 months) who underwent previous cardiac surgery.

The proportion of subjects with IE and underlying rheumatic heart disease decreased over time. Among the subjects with underlying CHD, postoperative IE increased from 25% (10/40) in era 1 to 62% (42/68) in era 3 ($P < 0.001$). In era 1, cardiopulmonary bypass was not available and thus postoperative IE occurred only after procedures performed without bypass (e.g., ligation of a PDA) or placement of a Blalock-Taussig shunt, whereas in era 3, 88% (37/42) of postoperative IE occurred after procedures performed with cardiopulmonary bypass. Early postoperative IE occurred in 70% (7/10) of the subjects in era 1, 18% (4/22) of the subjects in era 2, and 43% (18/42) of the subjects in era 3. In era 3, 44% (8/18) of such cases occurred within 2 weeks after surgery.

The proportion of subjects without known heart disease decreased between eras 2 and 3 (Table 1). However, the proportions of hospital-acquired IE and CVC use among such subjects were comparable.

Pathogens Causing IE

The pathogens causing IE during the three eras are shown in Table 2. Compared with era 1, the proportion of subjects infected with streptococcal species declined, whereas the proportion of those infected with staphylococcal spp. increased during the later eras. Furthermore, the proportion of IE cases caused by CoNS, gram-negative bacilli, and yeast increased in era 3 ($P < 0.001$), although the proportions of cases caused by *Candida* spp. were similar. Polymicrobial infections were relatively common in era 3, occurring in 14% (12/85) of subjects, most of whom (83%, 10/12) had a CVC in place when IE was diagnosed.

Hospital-Acquired Versus Community-Acquired IE in Era 3

In era 3, 72 subjects had underlying heart disease. Of these 72 subjects, 33 (46%) had high-risk lesions, 38 (53%) had moderate-risk lesions, and 1 (1%) had a low-risk lesion (i.e., a heart transplant) for IE [10]. The characteristics of the subjects with hospital-acquired IE are compared with the subjects with community-acquired IE during era 3 in Table 3. The median age at diagnosis was significantly lower among hospital-acquired cases than among community-acquired cases ($P < 0.001$). Almost all cases (29/31) of community-acquired IE were caused by gram-positive pathogens.

In era 3, fewer subjects had cyanotic heart disease than acyanotic heart disease (Table 3). All 20 children with cyanotic heart disease and 24 (46%) of the 52 children with acyanotic heart disease had lesions for which IE prophylaxis currently is recommended [37]. Among the 28 subjects for whom prophylaxis was not recommended, 13 (46%) had valvular disease and 11 (39%) had unrepaired left-to-right shunt lesions.

Echocardiographic findings consistent with IE and related to previously known cardiac disease were more common in the subjects with community-acquired IE (16/26, 62%) than in the subjects with hospital-acquired IE (13/46, 28%) ($P = 0.006$). All the subjects with an unrepaired PDA had hospital-acquired IE, and none had echocardiographic findings related to their lesion.

Crude Mortality and Complications

The crude mortality rate during the first half of era 1 (1930–1943, the so-called preantibiotic period) was 86%, and all the survivors had received sulfonamide agents. After the widespread availability of antibiotics in 1944, the crude mortality rate remained unchanged during the three eras. The crude mortality rates were 32% for era 1 (1944–1959), 21% for era 2, and 24% for era 3 ($P = 0.39$). Among the 20 subjects during era 3 who died, all had hospital-acquired IE, and 80% (16/20) had previously known heart disease, including four

premature infants with PDA and two patients who had previously undergone heart transplantation. In addition, of the 16 patients with known heart disease who died, 25% (4/16) had experienced early postoperative IE. The rates of crude mortality were similar for the subjects with cyanotic (20%, 4/20) and those with acyanotic (23%, 12/52) heart disease ($P = 1.00$), for the subjects currently recommended to receive antimicrobial prophylaxis (23%, 10/44) and those not recommended to receive it (21%, 6/28) ($P = 0.863$), and for the subjects with early (22%, 4/18) and those with late (8%, 2/24) postoperative IE ($P = 0.375$).

The morbidity associated with IE during the three eras is shown in Table 4. The overall complication rate was significantly lower in era 3 than in the earlier eras ($P = 0.004$). Among the 15 subjects with valvular insufficiency in era 3, 12 (80%) had IE caused by gram-positive pathogens, and 10 (67%) had community-acquired IE. The rates for morbidity were similar between the subjects with cyanotic (30%, 6/20) and those with acyanotic (33%, 17/52) heart disease ($P = 0.826$), and between the subjects recommended to receive IE prophylaxis (25%, 11/44) and those not recommended to receive it (43%, 12/28) ($P = 0.185$). However, the morbidity rate was higher among those with community-acquired IE (20/31, 65%) than among those with hospital-acquired IE (11/54, 20%) ($P < 0.001$). Only two subjects in era 3 had a second episode of IE, both caused by different pathogens than those that caused the first episode.

Discussion

Diagnosing Pediatric IE

The diagnosis of IE, historically a great challenge, changed during the study period due to improved echocardiographic and microbiologic diagnostic methods. The first widely used diagnostic criteria for IE were the von Reyn or Beth Israel criteria, which required pathologic proof for a case to be considered definitive IE [36]. Durack et al. [14] next developed the Duke criteria, which incorporated echocardiography and were subsequently modified largely to include additional microbiologic diagnostic criteria [24].

Investigators have sought to determine the applicability of the Duke and modified Duke criteria for pediatric IE. Del Pont et al. [11] retrospectively classified 38 pediatric patients with clinically suspected IE using the Duke criteria and found that 25 patients (66%) fulfilled the criteria for definite IE and 13 (34%) patients met the criteria for possible IE. Stockheim et al. [33] applied the Duke criteria to 111 children with a medical record discharge diagnosis of IE (who had been treated for IE) and determined that 73 (66%) were classified as definite and 38 (34%) as possible IE cases. Similarly, Tissieres et al. [35] applied the modified Duke criteria to 41 pediatric IE cases identified by a hospital diagnostic database and found that 36 (88%) were classified as definite and 5 (12%) as possible IE cases.

We chose to use the same case definitions in eras 2 and 3, which were compiled from previous case series of pediatric IE [31]. Our case definition largely used clinical and echocardiographic criteria, and it is likely, as described earlier [11,33,35], that the majority of our cases would be considered “definite” or “possible” using the Duke criteria.

Demographic and Clinical Characteristics of Children with IE

We were provided with a unique opportunity to study the epidemiology of pediatric IE over seven decades. To our knowledge, ours is the longest such series, although others also have described the changing epidemiology of pediatric IE [2,9,12,20,25,28,34]. We noted that the demographic characteristics of children with IE had changed. The proportion of males with IE increased during the later two eras, potentially due to the increased risk of CHD in males [4] and the increased risk of RHD in females [5].

The median age of the subjects with IE decreased during era 3 as improved diagnostic methods (e.g., echocardiography) [23], better supportive care (e.g., extracorporeal membrane oxygenation) [8], and advances in surgical techniques for young infants facilitated palliation for previously inoperable lesions (e.g., hypoplastic left heart syndrome) [6,19] and repair of certain lesions (e.g., tetralogy of Fallot and atrioventricular canal defect) at a younger age [27,30,32]. The proportion of subjects without known heart disease decreased between eras 2 and 3, potentially due to the increasingly widespread use of echocardiography and improved detection of mild cardiac anomalies.

Hospital-Acquired IE

In era 3, we noted that more than half of IE cases (64%, 54/85) were hospital-acquired and that most of these cases (85%, 46/54) involved children with underlying cardiac disease. Furthermore, early postoperative IE was more common in era 3. Other investigators also have noted an increase in early postoperative IE, potentially because of cardiopulmonary bypass requiring invasive monitoring as well as surgical interventions (e.g., valve replacement or conduit placement) resulting in persistent hemodynamic abnormalities [15,22]. In addition, CVC-associated bloodstream infections [29] can place a patient at risk for IE during the early postoperative period.

Pathogens Causing IE

As first noted in era 2 and observed in era 3, the relative proportion of streptococcal spp. decreased, whereas staphylococcal spp. increased. However, in era 3, more hospital-acquired pathogens were noted including CoNS, gram-negative bacilli, and yeast. Similar observations have been made by others [18,22]. We did not observe the hypothesized increase in vancomycin-resistant enterococci or methicillin-resistant *Staphylococcus aureus*, possibly due to the relatively low incidence of these pathogens in our children's hospital (P. Graham, personal communication).

Crude Mortality and Morbidity

Infective endocarditis remained associated with high rates of crude mortality and morbidity, although only subjects with hospital-acquired IE died in era 3, possibly due to their young age or their concomitant complex comorbid conditions. Yoshinaga et al. [38] demonstrated that among children with CHD and IE, age younger than 1 year, a vegetation size of 20 mm or larger, heart failure, and infection with *S. aureus* were independent predictors of mortality.

In the modern era, although the overall complication rate declined, complications were more common among subjects with community-acquired endocarditis. The increased risk of complications in these cases may be due to earlier diagnosis of hospital-acquired IE [21], increased embolic events in community-acquired IE [13], or confounding comorbid conditions in hospital-acquired IE that could obscure a diagnosis of IE-related complications.

IE Prophylaxis

Recent changes have been made in the recommendations for IE prophylaxis because most cases of IE are thought to occur after bacteremia from daily life events rather than after bacteremia from dental, surgical, or other invasive procedures. Furthermore, prophylaxis is now deemed reasonable for patients with the highest risk for adverse outcomes from IE rather than for those with an increased lifetime risk for acquiring IE [37]. Most of the subjects with CHD in era 3 had lesions for which IE prophylaxis was recommended, but IE did occur among patients for whom IE prophylaxis was not recommended.

This study was not designed to assess the efficacy of IE prophylaxis. We did not collect data related to antecedent procedures or compliance with prophylaxis in our pediatric cardiology population. However, no deaths could have been prevented by dental prophylaxis because all deaths occurred after hospital-acquired endocarditis.

Study Limitations

Because our hospital is a referral center for pediatric cardiology, our findings may not generalize to other populations at risk, and we could not determine population-based rates for pediatric IE. Case definitions and case findings changed over time. During era 1, all the subjects had heart disease, and modern diagnostic methods, particularly echocardiography, were unavailable. During eras 2 and 3, we used a clinical case definition for IE to allow comparability of the two eras and to reflect clinical practice. However, we did not use the Duke [14] or the modified Duke [24] criteria, which could have resulted in misclassification of some cases. Some patient-specific data were lacking for the subjects in eras 1 and 2. Finally, limited autopsies could have resulted in ascertainment bias.

Conclusions

The epidemiology of pediatric IE continues to evolve. Compared with children with IE in previous eras, the modern child with IE is younger and more likely to have congenital heart disease and postoperative IE, to have IE caused by a nonstreptococcal nonstaphylococcal pathogen, and to die if his or her diagnosis is hospital-acquired IE.

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References

1. Ashkenazi S, Levy O, Blieden L. Trends of childhood infective endocarditis in Israel with emphasis on children under 2 years of age. *Pediatr Cardiol* 2007;18:419–424. [PubMed: 9326687]
2. Awadallah SM, Kavey REW, Byrum CJ, Smith FC, Kveselis DA, Blackman MS. The changing pattern of infective endocarditis in childhood. *Am J Cardiol* 1991;68:90–94. [PubMed: 2058565]
3. Blumenthal S, Griffiths SP, Morgan BC. Bacterial endocarditis in children with heart disease. *Pediatrics* 1960;26:993–1017.
4. Campbell M. Incidence of cardiac malformations at birth and later, and neonatal mortality. *Br Heart J* 1973;35:189–200. [PubMed: 4570446]
5. Carapetis JR, McDonald M, Wilson NJ. Acute rheumatic fever. *Lancet* 2005;366:155–168. [PubMed: 16005340]
6. Chang RKR, Chen AY, Klitzner TS. Clinical management of infants with hypoplastic left heart syndrome in the United States, 1988–1997. *Pediatrics* 2002;110:292–298. [PubMed: 12165581]
7. Chu VH, Sexton DJ, Cabell CH, Reller LB, Pappas PA, Singh RK, Fowler VG Jr, Corey GR, Aksoy O, Woods CW. Repeat infective endocarditis: differentiating relapse from reinfection. *Clin Infect Dis* 2005;41:406–409. [PubMed: 16007540]
8. Cooper DS, Jacobs JP, Moore L, Stock A, Gaynor JW, Chancy T, Parpard M, Griffin DA, Owens T, Checchia PA, Thiagarajan RR, Spray TL, Ravishankar C. Cardiac extracorporeal life support: state of the art in 2007. *Cardiol Young* 2007;17(Suppl 2):104–115. [PubMed: 18039404]
9. Coward K, Tucker N, Darville T. Infective endocarditis in Arkansan children from 1990 through 2002. *Pediatr Infect Dis J* 2003;22:1048–1052. [PubMed: 14688563]
10. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, Gewitz MH, Shulman ST, Nouri S, Newburger JW, Hutto C, Pallasch TJ, Gage TW, Levison ME, Peter G, Zuccaro G Jr. Prevention of bacterial endocarditis: recommendations by the American Heart Association. *Circulation* 1997;96:358–366. [PubMed: 9236458]

11. Del Pont JM, de Cicco LT, Vartalitis C, Ithurralde M, Gallo JP, Vargas F, Gianantonio CA, Quirós RE. Infective endocarditis in children: clinical analyses and evaluation of two diagnostic criteria. *Pediatr Infect Dis J* 1995;14:1079–1086. [PubMed: 8745022]
12. Di Filippo S, Delahaye F, Semiond B, Celard M, Henaine R, Ninet J, Sassolas F, Bozio A. Current patterns of infective endocarditis in congenital heart disease. *Heart* 2006;92:1490–1495. [PubMed: 16818488]
13. Di Salvo G, Habib G, Pergola V, Avierinos JF, Philip E, Casalta JP, Vailloud JM, Derumeaux G, Gouvernet J, Ambrosi P, Lambert M, Ferracci A, Raoult D, Luccioni R. Echocardiography predicts embolic events in infective endocarditis. *J Am Coll Cardiol* 2001;37:1069–1076. [PubMed: 11263610]
14. Durack DT, Lukes AS, Bright DK. New criteria for diagnosis of infective endocarditis: utilization of specific endocardiographic findings. *Am J Med* 1994;96:200–209. [PubMed: 8154507]
15. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, Wilson W, Bolger AF, Bayer A, Levison ME, Pallasch TJ, Gage TW, Taubert KA. Unique features of infective endocarditis in childhood. *Pediatrics* 2002;109:931–943. [PubMed: 11986458]
16. Garvey GJ, Neu HC. Infective endocarditis: an evolving disease: a review of endocarditis at the Columbia-Presbyterian Medical Center 1968–1973. *Medicine Baltimore* 1978;57:105–127. [PubMed: 622043]
17. Giamarellou H. Nosocomial cardiac infections. *J Hosp Infect* 2002;50:91–105. [PubMed: 11846535]
18. Gilleece A, Fenelon L. Nosocomial infective endocarditis. *J Hosp Infect* 2000;46:83–88. [PubMed: 11049699]
19. Gutgesell HP, Gibson J. Management of hypoplastic left heart syndrome in the 1990s. *Am J Cardiol* 2002;89:842–846. [PubMed: 11909571]
20. Hansen D, Schmiegelow K, Jacobsen JR. Bacterial endocarditis in children: trends in its diagnosis, course, and prognosis. *Pediatr Cardiol* 1992;13:198–203. [PubMed: 1518737]
21. Hill EE, Herijgers P, Claus P, Vanderschueren S, Peetermans WE, Herregods MC. Clinical and echocardiographic risk factors for embolism and mortality in infective endocarditis. *Eur J Clin Microbiol Infect Dis* 2008;27:1159–1164. [PubMed: 18629556]
22. Karl T, Wensley D, Stark J, de Leval M, Rees P, Taylor JFN. Infective endocarditis in children with congenital heart disease: comparison of selected features in patients with surgical correction or palliation and those without. *Br Heart J* 1987;58:57–65. [PubMed: 3620243]
23. Leung MP, Mok CK, Lau KC, Lo R, Yeung CY. The role of cross-sectional echocardiography and pulsed Doppler ultrasound in the management of neonates in whom congenital heart disease is suspected: a prospective study. *Br Heart J* 1986;56:73–82. [PubMed: 3524633]
24. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T, Bashore T, Corey GR. Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. *Clin Infect Dis* 2000;30:633–638. [PubMed: 10770721]
25. Martin JM, Neches WH, Wald ER. Infective endocarditis: 35 years of experience at a children's hospital. *Clin Infect Dis* 1997;24:669–675. [PubMed: 9145742]
26. Massell BF, Chute CG, Walker AM, Kurland GS. Penicillin and the marked decrease in morbidity and mortality from rheumatic fever in the United States. *N Eng J Med* 1998;318:280–286.
27. Michielon G, Stellin G, Rizzoli G, Casarotto DC. Repair of complete common atrioventricular canal defects in patients younger than four months of age. *Circulation* 1997;96(Suppl):316–322. [PubMed: 9236451]
28. Normand J, Bozio A, Etienne J, Sassolas F, Le Bris H. Changing patterns and prognosis of infective endocarditis in childhood. *Eur Heart J* 1995;16(Suppl B):28–31. [PubMed: 7671921]
29. O'Grady NP, Alexander M, Dellinger EP, Gerberding JL, Heard SO, Maki DG, Masur H, McCormick RD, Mermel LA, Pearson ML, Raad II, Randolph A, Weinstein RA. Guidelines for the prevention of intravascular catheter-related infections. The Hospital Infection Control Practices Advisory Committee. Centers for Disease Control and Prevention. *U.S. Pediatr* 2002;110:e51.
30. Pigula FA, Khalil PN, Mayer JE, del Nido PJ, Jonas R. Repair of tetralogy of Fallot in neonates and young infants. *Circulation* 1999;100(2 Suppl):157–161.

31. Saiman L, Prince A, Gersony WM. Pediatric infective endocarditis in the modern era. *J Pediatr* 1993;6:847–853. [PubMed: 8501558]
32. Stellin G, Vida VL, Milanese O, Rizzoli G, Rubino M, Padalino MA, Bonato R, Casarotto D. Surgical treatment of complete A-V canal defects in children before 3 months of age. *Eur J Cardiothorac Surg* 2003;23:187–193. [PubMed: 12559341]
33. Stockheim JA, Chadwick EG, Kessler S, Amer M, Abdel-Hag N, Dajani AS, Shulman ST. Are the Duke criteria superior to the Beth Israel criteria for the diagnosis of infective endocarditis in children? *Clin Infect Dis* 1998;27:1451–1456. [PubMed: 9868659]
34. Takeda S, Nakanishi T, Nakazawa M. A 28-year trend of infective endocarditis associated with congenital heart diseases: a single institute experience. *Pediatr Int* 2005;47:392–396. [PubMed: 16091075]
35. Tissieres P, Gervaix A, Beghetti M, Jaeggi ET. Value and limitations of the von Reyn, Duke, and modified Duke for the diagnosis of infective endocarditis in children. *Pediatrics* 2003;112:e467–e471. [PubMed: 14654647]
36. von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. *Ann Intern Med* 1981;94:505–518. [PubMed: 7011141]
37. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M, Bolger A, Cabell CH, Takahashi M, Baltimore RS, Newburger JW, Strom BL, Tani LY, Gerber M, Bonow RO, Pallasch T, Shulman ST, Rowley AH, Burns JC, Ferrieri P, Gardner T, Goff D, Durack DT. Prevention of infective endocarditis: guidelines from the American Heart Association. *Circulation* 2007;116:1736–1754. [PubMed: 17446442]
38. Yoshinaga M, Niwa K, Niwa A, Ishiwada N, Takahashi H, Echigo S, Nakazawa M. Risk factors for in-patient mortality during infective endocarditis in patients with congenital heart disease. *Am J Cardiol* 2008;101:114–118. [PubMed: 18157976]

Table 1

Demographic and clinical characteristics of children with infective endocarditis (IE) diagnosed in three eras, 1930–2004

Characteristics	Era 1 1930–1959 (<i>n</i> = 58) <i>n</i> (%)	Era 2 1977–1992 (<i>n</i> = 62) <i>n</i> (%)	Era 3 1992–2004 (<i>n</i> = 85) <i>N</i> (%)
Males	19 (33)	39 (63)	43 (51)
Median age (years)	8 ^a	8.2	1.5
Range	3 months to 14 years	1 months to 19 years	6 days to 18.8 years
<2 years old	5 (9)	20 (32)	46 (54)
Prematurity	–	9 (15)	15 (18)
Underlying heart disease	58 (100)	43 (69)	72 (85)
Rheumatic heart disease	18	3	1
Congenital heart disease	40	40 ^b	68 ^b
Cardiac surgery	10	22	42
Early postoperative IE	7	4	18
Other	0	0	3 ^c
No known heart disease	0	19 (31)	13 (18)
Hospital-acquired IE	–	13	8
Central venous catheter	–	11	6

^a During era 1, children 15 years of age and older were admitted to the adult facility

^b Mitral valve prolapse occurred for 4 subjects in era 2 and 1 subject in era 3

^c Two subjects had undergone heart transplantation, and 1 subject had dilated cardiomyopathy

Table 2

Pathogens causing pediatric infective endocarditis (IE) during three eras, 1930–2004

Pathogens	Era 1 1930–1960 (<i>n</i> = 58) <i>n</i> (%)	Era 2 1977–1992 (<i>n</i> = 62) <i>n</i> (%)	Era 3 ^a 1992–2004 (<i>n</i> = 85) <i>n</i> (%)
Streptococcal spp.	40 (69)	14 (23)	26 (31)
<i>Staphylococcus aureus</i>	10 (17)	24 (39)	18 (21)
Methicillin-resistant <i>S. aureus</i>	0	8	4
Coagulase negative staphylococci	0	7 (11)	18 (21)
Enterococcal species	0	1 (2)	11 (13)
Vancomycin-resistant enterococci	–	–	0
Gram negative bacilli	0	4 (6)	10 (12)
<i>Candida</i> spp.	0	6 (10)	10 (12)
<i>Aspergillus</i> spp.	0	0	2 (2)
Culture negative	3 (5)	4 (6)	1 (1)
No blood culture obtained	5 (9)	0	0

^aTwelve subjects had polymicrobial infections

Table 3

Clinical characteristics and underlying heart disease requiring prophylaxis among subjects with infective endocarditis (IE) in era 3, 1992–2004

Clinical characteristics	Underlying heart disease (n = 72)		No known heart disease (n = 13)	
	Hospital-acquired IE (n = 46) n (%)	Community-acquired IE (n = 26) n (%)	Hospital-acquired IE (n = 8) n (%)	Community-acquired IE (n = 5) n (%)
Age				
Median	3.9 months	12.3 years	10.8 months	2.4 years
Age range	7 days to 12.6 years	4 months to 18.8 years	6 days to 15.5 years	6 months to 6 years
<2 years	34 (74)	5 (19)	5 (63)	2 (40)
Cardiac surgery	27 (57)	15 (54)	NA	NA
Central venous catheter	32 (70)	1 (4)	6 (75)	0
Pathogens (includes polymicrobial infections)				
Streptococcal spp.	5	16	1	4
<i>Staphylococcus aureus</i>	10	5	2	1
Coagulase negative staphylococci	13	1	4	0
Enterococcal spp.	9	2	0	0
Gram negative bacilli	8	1	1	0
<i>Candida</i> spp.	9	0	1	0
<i>Aspergillus</i> spp.	1	1	0	0
Cyanotic heart disease (n = 20)				
IE prophylaxis recommended	20			
Non-operated	5			
Conduit or shunt, persistent cyanosis	11			
Other cardiac surgery, persistent cyanosis	4			
Acyanotic heart disease (n = 52)				
IE prophylaxis recommended	24			
Prosthetic valve	10 ^a			
Prosthetic material	9			
Surgery within 6 months				
Surgical repair, residual defect	4			
Heart transplant with valvulopathy	1			
IE prophylaxis <i>not</i> recommended	28			
Valvular disease	13 ^b			
Patent ductus arteriosus	8 ^c			
Uncorrected ventricular septal	3			
Defect				
Repaired atroventricular canal	2			
Other	2 ^d			

^aIncludes 2 subjects with previous endocarditis. The prosthetic valves include 7 patients with homografts in the pulmonary position; 4 patients after the Ross procedure and 3 patients after truncus or pulmonary atresia with ventricular septal defect (VSD) repair

^b Includes 2 subjects with cardiomyopathy, 1 with mitral valve prolapse, and 1 with right coronary cusp prolapse and aortic regurgitation associated with an unrepaired VSD

^c All 8 were preterm infants with hospital-acquired IE, and 7 were unrepaired

^d Includes 1 subject with rheumatic heart disease and 1 subject with heart transplantation

Table 4

Complications of pediatric infective endocarditis during three eras, 1930–2004

Complications	Era 1 1930–1959 (<i>n</i> = 51) <i>n</i> (%)	Era 2 1977–1992 (<i>n</i> = 55) <i>n</i> (%)	Era 3 1992–2004 (<i>n</i> = 81) ^a <i>n</i> (%)
Overall rate ^b	26 (51)	37 (67)	31 (38)
Cardiac	8 (16)	10 (18)	19 (23)
Valvular insufficiency	–	9	15
Cardiac abscess	1	1	3
Myocardial infarction	2	–	0
Congestive heart failure	5	–	6
Pulmonary	15 (29)	9 (16)	9 (11)
Emboli	13	9	6
Pleural effusion	2	–	0
Central Nervous System	8 (16)	18 (33)	5 (6)
Emboli	7	9	4
Seizures	1	6	1
Meningitis	–	3	0
Other embolic events ^c	18 (35)	–	6 (7)

^aExcludes 4 subjects with a diagnosis determined by autopsy^bThe complication rate decreased over time ($P = 0.004$)^cOther included emboli to the kidneys ($n = 1$), spleen ($n = 1$), and extremities ($n = 4$)