Characteristics of Children Hospitalized With Infective Endocarditis

Michael D. Day, MD; Kimberlee Gauvreau, ScD; Stanford Shulman, MD; Jane W. Newburger, MD, MPH

Background—Infective endocarditis in children is rare, and most reports describe the experience in referral centers. The purpose of our study was to assess the characteristics of children with infective endocarditis in a large national sample.

Methods and Results—We analyzed hospital discharge records with International Classification of Diseases, ninth revision, codes indicating infective endocarditis among admissions of patients <21 years of age in the Kids’ Inpatient Databases 2000 and 2003; analyses for the 2 years were combined. In 1588 hospitalizations, the age distribution was bimodal, with peaks in infancy and late adolescence. The organism was coded in 632 admissions; Staphylococcus aureus was most common (57%), followed by the viridans group of streptococci (20%). Preexisting heart disease was present in 662 patients admitted (42%), among whom 81% had congenital heart disease, 8% had prosthetic valve endocarditis, and 5% had rheumatic heart disease. In-hospital mortality occurred in 84 patients (5%), 38 with preexisting heart disease. Mortality was 48% in the 25 patients with tetralogy of Fallot and pulmonary atresia, and 8% in the 54 patients with prosthetic valve endocarditis. Among 46 deaths without preexisting heart disease, S aureus was the causative organism in 13 of 14 patients (93%) beyond infancy; among 32 infants who died, 31% were premature.

Conclusions—In 2000 and 2003, we found a continuing shift in the epidemiology of pediatric infective endocarditis toward a higher proportion of children without preexisting heart disease. Risk factors for mortality included some forms of congenital heart disease and, among patients without preexisting heart disease, premature/ neonatal age and S aureus as an etiologic agent. (Circulation. 2009;119:865-870.)

Key Words: endocarditis ■ child, hospitalized ■ heart diseases ■ pediatrics

Infective endocarditis (IE) occurs less commonly in children than in adults, accounting for 1 in every 1300 to 2000 pediatric admissions annually.1,2 Although reported hospitalization rates for IE vary considerably among published series,3-7 the frequency of endocarditis among children appears to have increased in recent years.8-10 Furthermore, the epidemiology of IE in children has also evolved. Rheumatic heart disease, present in 30% to 50% of children with IE in the earliest pediatric series, is now a relatively uncommon substrate.3,9 In a large series of children with IE from 1977 to 1992, compared with a series from 1953 to 1972,3 mortality fell from 35% to 11%, the percent with rheumatic heart disease fell from 10% to 5%, and the percent of patients without underlying structural heart disease rose from 8% to 26%. A number of factors may be responsible for the changing epidemiology of IE: improvement in survival for patients with complex congenital heart disease (CHD), increasingly innovative surgical techniques, expansion of neonatal care for younger and smaller infants, and more frequent use of indwelling central venous catheters for the care of critically ill infants and children.10

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The purpose of our study was to assess the characteristics of children with IE in the current era in a large national sample. Specifically, we sought to describe the epidemiology of pediatric IE, to analyze risk factors for its occurrence, and to explore determinants of mortality. We pursued our goals by using the Healthcare Cost and Utilization Project Kids’ Inpatient Databases (KID) from 2000 and 2003.

Methods

Data Source

Data were obtained from the Healthcare Cost and Utilization Project KID 2000 and 2003. The KID was designed specifically to examine issues pertinent to healthcare delivery in children and consists of a stratified random sample of 2 516 833 discharges from 2784 institutions in 27 states in 2000 and 2 984 129 discharges from 3438 institutions in 36 states in 2003. Pediatric hospitals, academic medical centers, and specialty hospitals are included. The KID does not include all admissions from participating institutions but rather a 10% sample of uncomplicated in-hospital births and an 80% sample of complicated births and other pediatric discharges. Standard patient

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demographic data, institutional information, and up to 15 diagnosis and 15 procedure codes based on the International Classification of Diseases, ninth revision, clinical modification (ICD-9-CM), are included.

Data Analyses
All hospital discharges with ICD-9-CM diagnosis codes indicating IE (421.0, 421.1, 421.9, or 424.9) were selected. Cases in the sample were tabulated by patient and hospital characteristics. Because cases in 2000 and 2003 looked very similar, data from these 2 years were combined for subsequent analysis. Patient characteristics included age, gender, race/ethnicity (white, black, Hispanic, Asian/Pacific Islander, Native American, and other), median household income bracket (<$45 000, ≥$45 000), admission type (emergency, urgent, elective, newborn), expected primary payer (Medicare, Medicaid, private insurance including HMO, self-pay, no charge, or other), underlying type of heart disease (cardiomyopathy 425.xx; chronic rheumatic heart disease 393.xx-398.xx; CHD 745.xx-747.xx; heart replaced V42.1, V43.2; heart valve replaced V42.2, V43.3; cardiac device V45.0x), infecting organism (**codes and names**), outcomes of death, length of hospital stay, and total hospital charges. To accurately categorize patients with CHD, we used a hierarchical grading system. For those patients with >1 CHD diagnosis, the more complex diagnosis was used for further analysis.11 For example, a patient with both an atrial septal defect and tetralogy of Fallot would be classified as having tetralogy of Fallot.

Continuous variables are summarized using the median and interquartile range (IQR). Comparisons between groups (2000 versus 2003, teaching versus nonteaching hospitals, and free-standing children’s hospitals) were performed with the Wilcoxon rank-sum test for continuous variables.

The authors had full access to and take full responsibility for the integrity of the data. All authors have read and agree to the manuscript as written.

Results
The numbers of hospitalizations for IE among patients <21 years of age in the KID were 697 in 2000 and 891 in 2003. Because findings were similar in the 2 years examined, our analyses were performed on a data set combining these 2 years except as noted. Of the 1588 total admissions, 50.2% were male. Figure 1 depicts the incidence of hospitalization according to age for the 1480 of 1588 patients for whom age was identified. The median age at hospitalization was 12 years (range, 1 day to 20 years); the age distribution was bimodal, with peaks in infancy (31 days to 11 months of age) and the late teenage years (17 to 20 years of age). The race and ethnicity of children with IE did not differ significantly from those of all KID admissions. The median length of hospitalization was 10 days (IQR, 4 to 27 days). Although hospital length of stay was similar between 2000 and 2003, hospital charges appeared to rise over time (in 2000: median, $31 313; IQR, $11 079 to $98 650; in 2003: median, $45 218; IQR, $15 159 to $129 116; P<0.001).

Organisms
Codes for etiologic organisms, detailed in Figure 2, were available in 632 of the 1588 hospitalizations (32%). Staphylococcus aureus was the most common agent, followed by the viridans group of streptococci, other streptococci, and coagulase-negative staphylococci.

Type of Admitting Institution
Characteristics of admissions according to type of admitting hospital are summarized in Table 1. A small minority of admissions did not have teaching status coded (n=30), and some teaching hospital admissions (n=18) did not have children’s hospital status identified. Among 1558 admissions in which the teaching status of the hospital was classified, the majority (1220, 78.3%) were to teaching hospitals and the remainder (338, 21.7%) were to nonteaching hospitals. Among teaching institutions, 359 admissions were to free-standing children’s hospitals. Patients admitted to teaching compared with nonteaching hospitals tended to be younger, with a median age at admission of 10 versus 16 years (P<0.001). They also had longer median length of stay (12 versus 5 days; P<0.001), higher median hospital costs ($48 535 versus $15 636; P<0.001), a greater proportion of IE cases with preexisting heart disease (46.1% versus 26.3%; P<0.001), and a greater proportion with congenital cardiac surgery performed on the same admission (10.0% versus 0.6%; P<0.001). These differences were even greater when analyses were performed for free-standing children’s hospitals compared with all other teaching hospitals (Table 1).
Cardiac Status
Preexisting heart disease was present in 662 admissions (41.7%); the remaining 926 admissions (58.3%) had no codes for preexisting heart disease. Characteristics of admissions with and without preexisting cardiac disease are summarized in Table 2; those with preexisting heart disease codes had significantly longer and more costly hospital stays and a tendency toward higher in-hospital mortality. Among the 926 admissions without preexisting heart disease, associated conditions included neoplasms (88, 9.5%), prematurity (54, 5.8%), connective tissue disorders (52, 5.6%), and diabetes mellitus (22, 2.4%). Cardiac surgery was performed during the same hospitalization in 97 patients (10.5%); the most common procedure was aortic valve surgery (n/H11005 30, 30.9%).

Among the 662 admissions with preexisting heart disease, the majority (535, 80.8%) had codes for congenital heart lesions. Table 3 depicts the distribution of specific CHD diagnoses. Tetralogy of Fallot was the most common lesion, occurring in 106 of 535 admissions (19.8%) with CHD codes. Diagnoses in the remaining patients, ie, with preexisting heart disease but without CHD, included 75 (4.7%) with previous rheumatic heart disease, 54 (3.4%) with prosthetic valves, 49 (3.1%) with cardiomyopathy, and 22 (1.4%) with intracardiac devices, comprising defibrillators or pacemakers. Some of the 127 admissions without CHD had multiple cardiac codes. Admissions with and without CHD codes had similar age and gender distributions.

Among all patients with preexisting heart disease, 33.8% (224 of 662) had some form of cardiac surgery performed on the same admission, and 55.4% of the cardiac surgeries performed (124 of 224) were congenital heart surgery. In these 124 patients, endocarditis occurred on the same admission as congenital heart disease. The most common coded organism, followed by the viridans group streptococci and coagulase-negative staphylococci. The other organisms occurred relatively infrequently.

Figure 2. Pie chart showing the number and percentage of IE admissions in the KID from 2000 and 2003 with a coded causative organism. S aureus was the most common coded organism, followed by the viridans group streptococci and coagulase-negative staphylococci. The other organisms occurred relatively infrequently.

Table 1. Characteristics According to Type of Admitting Hospital

<table>
<thead>
<tr>
<th>Variable</th>
<th>Type of Hospital*</th>
<th></th>
<th></th>
<th>Type of Teaching Hospital†</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Nonteaching (n=338)</td>
<td>Teaching (n=1220)</td>
<td></td>
<td>Not Free-Standing Children's (n=843)</td>
<td>Free Standing Children's (n=359)</td>
<td></td>
</tr>
<tr>
<td>Age at admission, median (IQR), y</td>
<td>16 (4–19)</td>
<td>10 (1–17)</td>
<td>&lt;0.001</td>
<td>12 (1–18)</td>
<td>6 (0–13)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Length of stay, median (IQR), d</td>
<td>5 (3–13)</td>
<td>12 (5–30)</td>
<td>&lt;0.001</td>
<td>11 (5–26)</td>
<td>14 (6–38)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Total hospital charges (IQR), median, $</td>
<td>15 636 (8160–44 302)</td>
<td>48 535 (17 022–135 745)</td>
<td>&lt;0.001</td>
<td>43 514 (14 512–121 511)</td>
<td>63 517 (24 390–188 394)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death, n (%)</td>
<td>12 (3.6)</td>
<td>72 (5.9)</td>
<td>0.2</td>
<td>50 (5.9)</td>
<td>20 (5.6)</td>
<td>0.33</td>
</tr>
<tr>
<td>Preexisting cardiac disease, n (%)</td>
<td>89 (26.3)</td>
<td>562 (46.1)</td>
<td>&lt;0.001</td>
<td>347 (41.2)</td>
<td>208 (57.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Congenital cardiac surgery, n (%)</td>
<td>¥ (0.6)</td>
<td>122 (10.0)</td>
<td>&lt;0.001</td>
<td>67 (8.0)</td>
<td>55 (15.3)</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Thirty admissions could not be classified with respect to whether they occurred at teaching or nonteaching hospitals.
† Eighteen admissions could not be classified with respect to whether they occurred at free-standing children's hospitals because children's hospital status was not available.
¥ ≤10.
genital heart surgery; the database did not allow us to determine whether surgery occurred before or after the diagnosis of IE.

**Prosthetic Valve Endocarditis**

Prosthetic valve endocarditis occurred in 54 of 662 admissions (8.2%) with preexisting heart disease. Among these, 11 (20.4%) underwent prosthetic valve replacement during the same admission. The causative organism was coded in 29 cases (53.7%). *S aureus* was the most common organism, coded in 11 of 29 patients (37.9%). The viridians group of streptococci was present in 27.6% of patients, and coagulase-negative staphylococci in 17.2%. Patients admitted with prosthetic valve endocarditis were older than those without this diagnosis (median age, 18.8 years [range, 2.5 to 20 years]; \( P < 0.001 \)).

**Mortality**

Inpatient mortality occurred in 84 admissions (5.3%), including 46 without preexisting heart disease codes and 38 with preexisting heart disease codes. Patients who died had longer hospital stay (median, 18 versus 10 days; \( P < 0.001 \)) and more costly hospitalization (median, $139,266 versus $36,504; \( P < 0.001 \)).

Among 46 patients who died without preexisting heart disease codes, 32 (69.5%) were infants; their median age was 66 days (range, 1 day to 11 months). Of these 32 infants, 31.2% were premature. The mortality rate for premature infants was significantly higher than that for older infants and children (13.3% versus 4.5%, \( P < 0.001 \)). Among 14 patients whose deaths occurred after infancy, *S aureus* was the causative organism in 13 (93%), significantly greater (\( P < 0.001 \)) than the mortality rate for all other coded organisms in patients without preexisting heart disease (22 of 260, 8.5%).

Table 3 summarizes the in-hospital mortality rates among IE cases with preexisting CHD according to diagnostic group. Among the 54 patients with prosthetic valve endocarditis, 7.4% died. Death occurred in 8.1% of 124 patients with preexisting heart disease who underwent congenital heart surgery during the same admission. The mortality rate was only 1% in the 96 admissions with a diagnosis of ventricular septal defect.

### Table 3. Admissions and Deaths According to CHD Diagnosis

<table>
<thead>
<tr>
<th>CHD Diagnosis*</th>
<th>IE Admissions, ( n )</th>
<th>Mortality for Diagnosis, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>535</td>
<td>6.7</td>
</tr>
<tr>
<td>TOF</td>
<td>106</td>
<td>18.9</td>
</tr>
<tr>
<td>TOF/PS</td>
<td>81</td>
<td>9.9</td>
</tr>
<tr>
<td>TOF/PA</td>
<td>25</td>
<td>48.0</td>
</tr>
<tr>
<td>VSD</td>
<td>97</td>
<td>1.0</td>
</tr>
<tr>
<td>Hypoplastic left heart syndrome</td>
<td>51</td>
<td>7.8</td>
</tr>
<tr>
<td>Congenital aortic regurgitation</td>
<td>43</td>
<td>0</td>
</tr>
<tr>
<td>D-transposition of the great arteries</td>
<td>33</td>
<td>9.1</td>
</tr>
<tr>
<td>Patent ductus arteriosus</td>
<td>27</td>
<td>0</td>
</tr>
<tr>
<td>Atrial septal defect</td>
<td>20</td>
<td>0</td>
</tr>
<tr>
<td>Complete AV canal</td>
<td>19</td>
<td>15.8</td>
</tr>
<tr>
<td>Tricuspid atresia</td>
<td>18</td>
<td>0</td>
</tr>
<tr>
<td>Coarctation of the aorta</td>
<td>17</td>
<td>17.6</td>
</tr>
<tr>
<td>Interrupted aortic arch/VSD</td>
<td>17</td>
<td>11.8</td>
</tr>
<tr>
<td>CHD (NOS)</td>
<td>16</td>
<td>0</td>
</tr>
<tr>
<td>Congenital aortic stenosis</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Truncus arteriosus</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>L-transposition of the great arteries</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Totally anomalous pulmonary venous return</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Congenital mitral regurgitation</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Subaortic stenosis</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>Ebstein’s anomaly</td>
<td>↑</td>
<td>0</td>
</tr>
<tr>
<td>PS</td>
<td>↑</td>
<td>0</td>
</tr>
</tbody>
</table>

*TOF indicates tetralogy of Fallot; PS, pulmonary stenosis; PA, pulmonary atresia; VSD, ventricular septal defect; AV, atrioventricular; and NOS, not otherwise specified.

*Diagnoses are mutually exclusive (no patients are in >1 category).

†≤10 observations.
Discussion

Using the KID 2000 and 2003, we found that IE was a relatively infrequent diagnosis in hospitalized children in the United States. IE was coded most commonly in infants and late adolescents. The similar frequency in male and female patients in our analyses stands in contrast to the male predominance in infections in general and IE specifically.\textsuperscript{12–14} We found that \textit{S aureus} was the most common causative organism and that prosthetic valve IE was caused by organisms similar to those affecting patients without prosthetic valves; these data are consistent with other recent reports on IE.\textsuperscript{1,2,14} The mortality rate in the KID, 5.3\%, was lower than that reported in the adult population (18\% to 23\%).\textsuperscript{15,16} In recent pediatric IE series from large clinical centers caring for children with the most complex forms of CHD (10\% to 11\%).\textsuperscript{6–7,17} Interestingly, IE cases at teaching institutions had higher inpatient mortality and were more likely to have had preexisting heart disease. Inpatient mortality approached 50\% for those with tetralogy of Fallot with pulmonary atresia. Among those without preexisting heart disease, risk factors for mortality included premature/neonatal age and \textit{S aureus} as the causative organism.

Prior reports have suggested that endocarditis is occurring in fewer children with rheumatic heart disease, commensurate with its declining prevalence, and in a greater proportion of children without preexisting heart disease.\textsuperscript{1,4,6–8} These secular trends continued in our present analysis, in which only 4.7\% had rheumatic heart disease and the percent of admissions without preexisting heart disease rose to a striking 56\%. The higher proportion without preexisting heart disease may reflect the KID’s nationally representative composition of hospitals compared with single centers with a referral bias for CHD. It is also possible that increasing use of in-dwelling catheters in chronically ill children without preexisting heart disease is contributing to the changing epidemiology of IE. Our data also show a trend toward a growing number of younger patients with IE, perhaps related to the increased proportion of IE cases who are premature infants without preexisting heart disease.

In the most recent American Heart Association guidelines on prevention of IE, antibiotic prophylaxis is recommended only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome should they acquire IE.\textsuperscript{18} Formulation of these guidelines was particularly challenging in CHD because there are limited national data on risk factors for adverse outcomes. We thus explored mortality rates according to congenital heart lesion. Patients with tetralogy of Fallot and pulmonary atresia had the highest mortality rate, a remarkable 48\%. Unfortunately, our ability to further characterize risk factors within this and other diagnostic groups was limited by data available in the KID and by the small number of deaths. However, children with tetralogy of Fallot and pulmonary atresia most often have right-ventricular-to-pulmonary-artery homografts containing valves and thereby would be classified in the group requiring dental prophylaxis in the latest AHA guidelines. Furthermore, patients with the most severe forms of tetralogy of Fallot and pulmonary atresia cannot undergo closure of their ventricular septal defects and remain cyanotic, another criterion for use of endocarditis prophylaxis. The increased prevalence of IE in patients with tetralogy of Fallot raises the possibility that DiGeorge syndrome might be a risk factor. Because we do not know whether genetic testing was routinely performed in these patients at all centers, we were unable to pursue this hypothesis using the KID.

Our data should be viewed in light of additional limitations. The KID is an administrative database that does not include individual patient identifiers. Therefore, we could not determine how many hospitalizations were IE readmissions or transfers between hospitals. Misdiagnosis and improper coding may have caused an underestimation or overestimation of IE cases, and the extent to which miscoding may have contributed to our study inferences is unknown. For example, incomplete coding of preexisting conditions may have increased the proportion of patients without preexisting heart disease codes in the KID. We cannot exclude the possibility that nonteaching and teaching hospitals differed in their tendency to miscode cases or differed with respect to some other reporting bias. Data were incompletely coded for some variables, particularly for causative organism. Furthermore, we were unable to recognize what proportion of \textit{S aureus} infections were methicillin resistant. Because detailed clinical information is missing from coded data, we cannot determine the criteria used to diagnose IE cases. We cannot exclude the possibility that some children without preexisting heart disease may have had undetected mild heart disease such as bicuspid aortic valve. However, most forms of heart disease that place children at risk for IE should have been detected by echocardiography, which is performed as standard of care in patients with a diagnosis of IE. Finally, we could not ascertain mortality for cases after hospital discharge.

Conclusions

Our data suggest a continuing shift in the epidemiology of pediatric IE toward a higher proportion of children without preexisting heart disease. Mortality among patients without preexisting heart disease was greatest in those with premature/neonatal age and \textit{S aureus} as an etiologic agent. In patients with preexisting heart disease, mortality was greatest for those with tetralogy of Fallot and pulmonary atresia. In the future, surveillance using administrative databases and more detailed record review may be useful in ascertaining whether adoption of the 2007 AHA IE prophylaxis guidelines has changed the prevalence of pediatric IE.

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Disclosures

None.

References

Infective endocarditis (IE) can be a lethal and devastating disease in children. Great efforts have been made in the past half a century at identifying those children at greatest risk for developing IE and trying to implement strategies to protect them through prophylaxis. Likewise, efforts have been made at understanding the most prevalent pathogens responsible for the disease so that proper antibiotic therapy can be initiated once the diagnosis is made. Our understanding of the current epidemiology has been hampered in part because many of the published series on IE reflect the experience of single referral centers. Our study looks to draw a more global picture of IE by using the Kid’s Inpatient Database, drawing on discharge information from teaching and nonteaching institutions around the United States. It is our hope that these data can be helpful in gaining a better understanding of patients with IE, particularly those who are at highest risk for mortality. Armed with this knowledge, we hope that hypotheses can be generated from these data to better identify and treat patients with IE.
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In regards to the article by Day et al, “Characteristics of Children Hospitalized With Infective Endocarditis,” which appeared in the February 17, 2009 issue of the journal (*Circulation*. 2009;119:865–870), the authors have released the following statement:

“Our study, ‘Characteristics of Children Hospitalized with Infective Endocarditis,’ published in *Circulation* in 2009, is an analysis of the Kids Inpatient Database (KID), a large, restricted-access, publicly available dataset that is maintained by the Agency for Healthcare Research and Quality (AHRQ). One of the provisions of the KID Data Use Agreement is that no data observation involving 10 or fewer observations is to be published. This measure was put in place by AHRQ to protect individual patients’ privacy and to prevent the potential disclosure of personal information. Although we are confident that this manuscript could not be used to identify individuals or their personal information, some tabulated cells contain 10 or fewer observations, in inadvertent violation of the Data Use Agreement. We are therefore posting a revised online version of our paper that is in compliance with the AHRQ guidelines, and request that, going forward, authors cite the corrected version of our manuscript.”

The correction has been made to the current online version of the manuscript. The authors regret the error.

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