Pediatric infective endocarditis: Has *Staphylococcus aureus* overtaken viridans group streptococci as the predominant etiological agent?

Aisha Alshammary MD, Marilou Hervas-Malo MSc, Joan L Robinson MD

**BACKGROUND:** Viridans group streptococci (VGS) have traditionally been the most common etiological agents of infective endocarditis (IE). Advances in cardiovascular surgery and the increasing use of long-term central venous catheters may have altered the epidemiology of pediatric IE.

**METHODS:** A chart review of children younger than 17 years of age with IE was completed at the Stollery Children’s Hospital (Edmonton, Alberta) between 1985 and 2004. The literature was reviewed to look for changes over time in the most common etiological agents of pediatric IE.

**RESULTS:** There were 31 cases of definite IE and nine cases of possible IE at the Stollery Children’s Hospital, 19 of which were nosocomial. Thirty cases (75%) had congenital heart disease. The etiological agents were *Staphylococcus aureus* (n=16), VGS (n=5), coagulase-negative staphylococci (n=3), enterococci (n=3), other streptococci (n=8), *Enterobacter cloacae* (n=1) and *Stenotrophomonas maltophilia* (n=1), while three cases were culture negative. Two deaths were due to *S. aureus* IE. Review of the literature identified an increasing number of case series in which *S. aureus* was the predominant etiological agent, but VGS still predominated in some recent series.

**CONCLUSION:** Congenital heart disease remains the primary risk factor for pediatric IE. Prospective population-based studies are required to determine whether *S. aureus* has become the predominant pathogen.

**Key Words:** Cardiac; Endocarditis; *Staphylococcus aureus*; Viridans group streptococci

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**Endocardite infectieuse pédiatrique : *Staphylococcus aureus* supplante-t-il les streptocoques du groupe *Viridans* comme agent étiologique prédominant?**

**HISTORIQUE :** Les streptocoques du groupe Viridans (SGV) ont longtemps été les agents étiologiques les plus souvent impliqués dans l’endocardite infectieuse (EI). Mais les progrès de la chirurgie cardiovasculaire et l’emploi croissant des cathéters veineux centraux à demeure pourraient avoir modifié l’épidémiologie de l’EI pédiatrique.

**METHODE :** Une analyse des dossiers d’enfants de moins de 17 ans atteints d’EI a été effectuée au Stollery Children’s Hospital (Edmonton, Alberta) entre 1985 et 2004. Une revue de la littérature a permis de retracer les changements quant aux agents étiologiques les plus couramment rencontrés dans l’EI pédiatrique au fil des ans.

**RÉSULTATS :** Trente-et-un cas d’EI avérée et neuf cas d’EI possible ont été dénombrés au Stollery Children’s Hospital; 19 étaient d’origine nosocomiale. Trente cas (61 %) souffraient de maladie cardiaque congénitale. Les agents étiologiques étaient *Staphylococcus aureus* (n = 16), les SGV (n = 5), le *Staphylococcus coagulase-négatif* (n = 3), les *entérocoques* (n = 3), d’autres streptocoques (n = 8), *Enterobacter cloacae* (n = 1) et *Stenotrophomonas maltophilia* (n = 1), tandis que trois cas ont obtenu des résultats de culture négatifs. Deux décès ont été attribuables à une EI à *S. aureus*. La revue de la littérature a permis de relever un nombre croissant de séries de cas dans lesquels *S. aureus* était l’agent étiologique prédominant, mais le GVST restait prépondérant dans certaines séries récentes.

**CONCLUSION :** La maladie cardiaque congénitale reste le principal facteur de risque d’EI pédiatrique. Il faudra réaliser des études de population prospectives pour déterminer si *S. aureus* est devenu l’agent pathogène prédominant.

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TABLE 1

Organisms isolated from blood cultures or heart tissues in 40 children with infective endocarditis

<table>
<thead>
<tr>
<th>Organism</th>
<th>Isolate</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Staphylococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>16</td>
<td>(40)</td>
</tr>
<tr>
<td>Coagulase-negative staphylococci</td>
<td>3</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Streptococci</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Viridans</td>
<td>5</td>
<td>(12.5)</td>
</tr>
<tr>
<td>Enterococci</td>
<td>3</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Pneumococci</td>
<td>3</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Beta-hemolytic (group A [n=2]; group B [n=1])</td>
<td>3</td>
<td>(7.5)</td>
</tr>
<tr>
<td>Other streptococci*</td>
<td>2</td>
<td>(5)</td>
</tr>
<tr>
<td>Gram-negative organisms</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Enterobacter cloacae</td>
<td>1</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Stenotrophomonas maltophilia</td>
<td>1</td>
<td>(2.5)</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Culture negative</td>
<td>3</td>
<td>(7.5)</td>
</tr>
</tbody>
</table>

* Aerococcus (n=1), Abiotrophia (n=1)

more of the following International Classification of Disease – Ninth Revision clinical modification codes: 036.42, meningococcal endocarditis; 083.0, Q fever; 098.84, gonococcal endocarditis; 112.81, candidal endocarditis; 115.94, histoplasmosis endocarditis; 421.0, acute and subacute bacterial endocarditis; 421.1, acute and subacute infective endocarditis in disease classified elsewhere; or 421.9, acute endocarditis, unspecified.

Data were collected on underlying medical conditions including CHD, recent surgery or cardiac catheterization, and blood culture results. The presence or absence of a CVC was recorded in children without CHD who developed IE. Cases of IE in children younger than six months of age were analyzed separately to determine whether the etiological agents varied in this age group. Data were collected on the presence and duration of a fever (temperature higher than 38.2°C) or the presence of a secondary fever (defined as recurrence of fever after being afebrile for more than 48 h) and the suspected reason for the fever. The need for surgery to treat IE, the duration and route of antibiotic administration and survival to hospital discharge were recorded. More detailed outcome data could not be collected because many patients were discharged to distant hospitals.

RESULTS

Demographics

The International Classification of Disease – Ninth Revision codes at the Stollery Children’s Hospital identified 75 patients, 40 of whom fit the inclusion criteria (23 boys and 17 girls ranging from two weeks to 16 years of age, with a median age of two years). There were 31 cases of definite IE (10 based on pathological criteria and 21 on clinical criteria) and nine cases of possible IE.

Predisposing cardiac conditions

Twenty-eight of 40 IE patients (70%) had previously diagnosed CHD (ventricular septal defect [VSD], n=3; VSD with other defects, n=17; coarctation of the aorta, n=2; bicuspid aortic valve, n=2; pulmonary stenosis, n=2; transposition of the great arteries, n=1 and mitral valve prolapse [MVP], n=1), two (5%) had previously undiagnosed CHD (MVP and VSD) and 10 (25%) had a normal heart. Of the 10 cases with a normal heart, four had no IE risk factors and the other six had a severe burn, an infected cystic hygroma with a CVC, Crohn’s disease with a CVC, cerebral palsy with recurrent pneumococcal bacteremia, excoriated skin from infected eczema and necrotizing enterocolitis. None of the patients had a history of intravenous drug use. Previous cardiac surgery had been performed in 21 of 30 children with CHD (70%), with 16 of these 21 children having surgery within six months before the onset of IE. The cardiac lesions in the eight children with known CHD but no previous cardiac surgery included VSD (n=4), MVP and mitral regurgitation (n=1), pulmonary stenosis (n=1), bicuspid aortic valve and aortic stenosis (n=1), and Tetralogy of Fallot (n=1).

Etiological agents

Blood cultures were positive for the suspected etiological agent in 37 of 40 cases (93%) of IE (Table 1), with 16 (40%) due to methicillin-sensitive Staphylococcus aureus and none due to methicillin-resistant S. aureus. There were three cases of culture-negative IE. The etiological agents in the 10 children with normal
The predominance of *S. aureus* (n=3), enterococcus (n=1), VGS (n=1), Abiotrophia (n=1), pneumococcus (n=1), group A streptococcus (n=1) and *Enterobacter cloacae* (n=1). The features of children with *S. aureus* IE are compared with those with other etiological agents in Table 2, with there being a trend toward an increased incidence of nosocomial infections in those with *S. aureus* IE. Over the 19 years of the study, there was an increase in the number of cases of IE but no significant change in the incidence of *S. aureus* IE (Table 3).

Ten cases of IE occurred in children younger than six months of age (10 of whom had CHD), with the etiological agents being *S. aureus* (n=4), enterococcus (n=3), coagulase-negative staphylococci (n=2), *Streptococcus agalactiae* (n=1) and *Stenotrophomonas* (n=1). All were nosocomial. The only statistically significant difference from older children was that the incidence of enterococcal IE was higher (P=0.017).

**NOSOCOMIAL INFECTION**
Seventeen of 28 cases (61%) in children with known CHD were nosocomial (*S. aureus* n=10), coagulase-negative staphylococci n=3), enterococcus n=2), *Stenotrophomonas* n=1), and culture negative n=1), with IE occurring a median of eight days (range zero to 72 days) following cardiac surgery or cardiac catheterization – eight cases occurring within eight days of cardiac surgery, seven cases occurring 14 to 73 days after cardiac surgery, and two cases (both with *S. aureus*) occurring within four days after diagnostic cardiac catheterization.

**HOSPITAL COURSE AND OUTCOME**
Fever occurred in 37 of 40 patients for a median of four days before diagnosis and for a median of one day after appropriate antibiotics were started (range zero to 21 days). Among the 12 patients who had fever daily for five or more days after appropriate antibiotics were started, eight had complicated courses (seven had possible emboli and one had an aortic ring abscess). Their etiological agents were *S. aureus* (n=4), VGS (n=1), pneumococcus (n=1), *E. cloacae* (n=1) and culture negative (n=1). Secondary fever occurred in seven cases and was never attributed to IE.

Surgery for IE was performed in 11 cases (27.5%) (four valve replacement, one VSD homograft replacement, four valve repair and two vegetation removal), a median of 17 days (range three days to nine months) following diagnosis of IE. The etiological agent was *S. aureus* in three of these 11 cases. Death occurred in two patients with *S. aureus* IE (a two-month-old girl who developed IE following cardiac catheterization and a nine-year-old boy who had a mitral valve vegetation diagnosed eight days following cardiac surgery and died of intracranial hemorrhage five days later).

All survivors received a minimum of four weeks intravenous antibiotics (range 28 to 90 days), with the longest course being in a child with infected prosthetic material that could not be removed. Antibiotics were administered via a peripheral intravascular catheter only (n=2) or primarily by a conventional CVC (n=24), a peripherally inserted CVC (n=11) or both kinds of CVC (n=3). There were no recurrences of IE, although a patient with *S. agalactiae* (group B streptococcus) IE received 14 days of intravenous antibiotics for group B streptococcus bacteremia 44 days before the diagnosis of IE. Oral antibiotics were not used for therapy of IE, except for long-term suppression in the child with the infected prosthetic material with long-term follow-up not being available. Six of the 40 patients were in the intensive care unit at the time of diagnosis for a median intensive care unit stay of 16 days (range three to 27 days) after diagnosis of IE.
agents of adult IE from 1970 to 2000, with VGS still being
(22) in Minnesota, USA, showed no change in the causative
correction of CHD (21). However, a population-based study
to more invasive surgical procedures being performed for
tries, showed
16
116 children (79%) had congenital heart
disease (CHD), but it is not specified how many had surgery; §20 children (87%) had CHD, but it is not specified how many had surgery; ¶22 children (88%) had
etiological agents were NR for three children (11,18) and nine children had two pathogens each (11,13); ***34 children (74%) ha d CHD, but it is not specified how
manner such high rates of infection for such long periods. The
Data in Table 4 is presented in an order of increasing a
yearly basis, whereas the clinicopathologic series (16) and
series, versus rates as low as 37% in previous pediatric stud-
ies (16). However, these differences are likely accounted for by
variations in the definition chosen for IE, and it is possible that
cases of culture-negative IE were missed by our definition.
In an adult study (23) of 105 valves excised due to IE, pathogens
were identified by polymerase chain reaction in 64 valves but
by culture in only 14 valves, likely because patients had
received effective antibiotics that sterilized the valve or had
pathogens that were difficult to culture. Determining the etio-
logic agent of IE is likely to be more accurate once molecular
testing of blood or excised tissue for multiple organisms
becomes more practical. As has been previously described,
tenterococcal IE occurred only in children younger than
the etiological agents of pediatric IE may be changing. The
2000 modification of the Duke criteria added community-
acquired S aureus bacteremia as a major criterion (19) (the
original version accepted only nosocomial S aureus bac-
teriaemia as a major criterion) – recognizing that many cases of
S aureus IE are now community acquired, including six of the
16 S aureus cases in the current study. A registry of cases of
adult IE between 2000 and 2003, from 16 developed coun-
tries, showed S aureus to be the predominant pathogen,
accounting for 558 of 1779 cases (31.4%) (20). Recent IE
guidelines mentioned that the incidence of S aureus IE seems
to be increasing, and postulated that this could be secondary
to more invasive surgical procedures being performed for
perforation of CHD (21). However, a population-based study
(22) in Minnesota, USA, showed no change in the causative
agents of adult IE from 1970 to 2000, with VGS still being
predominant. Therefore, it is possible that S aureus IE
over-represented in studies, such as the present one, in
which many of the cases of IE occurred in the postoperative
period.

Blood cultures were positive in almost all cases in the pres-
ent study, versus rates as low as 37% in previous pediatric stud-
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</thead>
<tbody>
<tr>
<td>Number of children</td>
<td>149</td>
<td>26</td>
<td>64</td>
<td>63</td>
<td>23</td>
<td>44</td>
<td>25</td>
<td>48</td>
<td>76</td>
<td>62</td>
<td>161</td>
</tr>
<tr>
<td>CHD with no previous surgery, n (%)</td>
<td>NR†</td>
<td>8 (31)</td>
<td>49 (77)</td>
<td>1 (28)</td>
<td>NR‡</td>
<td>18 (41)</td>
<td>NR†</td>
<td>24 (50)</td>
<td>14 (19)</td>
<td>18 (29)</td>
<td>5 (31)</td>
</tr>
<tr>
<td>CHD with previous surgery, n (%)</td>
<td>NR†</td>
<td>14 (54)</td>
<td>14 (22)</td>
<td>7 (20)</td>
<td>NR‡</td>
<td>26 (59)</td>
<td>NR†</td>
<td>24 (50)</td>
<td>48 (66)</td>
<td>22 (35)</td>
<td>4 (25)</td>
</tr>
<tr>
<td>RHD, n (%)</td>
<td>14 (9)</td>
<td>1 (4)</td>
<td>1 (2)</td>
<td>0 (0)</td>
<td>1 (4)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4 (5)</td>
<td>3 (5)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Normal heart, n (%)</td>
<td>17 (11)</td>
<td>3 (11)</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>2 (9)</td>
<td>0 (0)</td>
<td>3 (12)</td>
<td>0 (0)</td>
<td>7 (10)</td>
<td>19 (31)</td>
<td>7 (44)</td>
</tr>
<tr>
<td>Staphylococcus aureus, n (%)</td>
<td>41 (27)</td>
<td>3 (11)</td>
<td>12 (19)</td>
<td>6 (17)</td>
<td>8 (35)</td>
<td>14 (32)</td>
<td>2 (18)</td>
<td>13 (27)</td>
<td>24 (31)</td>
<td>24 (39)</td>
<td>7 (29)</td>
</tr>
<tr>
<td>VGS, n (%)</td>
<td>64 (45)</td>
<td>13 (50)</td>
<td>23 (36)</td>
<td>16 (46)</td>
<td>9 (39)</td>
<td>17 (39)</td>
<td>9 (40)</td>
<td>14 (29)</td>
<td>29 (38)</td>
<td>22 (35)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Culture negative, n (%)</td>
<td>19 (13)</td>
<td>1 (4)</td>
<td>19 (30)</td>
<td>10 (28)</td>
<td>1 (4)</td>
<td>3 (7)</td>
<td>3 (12)</td>
<td>5 (10)</td>
<td>5 (6)</td>
<td>4 (6)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Other organisms, n (%)</td>
<td>5 (16)§§</td>
<td>36 (37)</td>
<td>8 (18)¶¶¶</td>
<td>6 (29)</td>
<td>31 (54)****</td>
<td>9 (36)††††</td>
<td>16 (40)</td>
<td>247 (27)</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Years of study not reported (NR) so publication year reported. †Only infants younger than three months of age enrolled. ‡18 children (79%) had congenital heart disease (CHD), but it is not specified how many had surgery; §20 children (87%) had CHD, but it is not specified how many had surgery; ¶22 children (88%) had CHD, but it is not specified how many had surgery; ††3 (6%) were fungi; ‡‡One case died before blood cultures sent and two cases had two organisms each; §§Coagulase-negative staphylococci n=2 (8%), enterococcus n=1 (4%), group A streptococcus n=1 (4%), HACEK (Haemophilus, Actinobacillus, Cardiobacterium, Eikenella corrodens and Kingella species) n=1 (4%), Aspergillus n=1 (2%), Pseudomonas n=1 (2%), Staphylococcus albus n=2 (5%), Salmonella n=1 (2%); ****Enterococcus n=9 (16%), other streptococci n=6 (14%), Gram-negative n=7 (12%), coagulase-negative staphylococci n=4 (7%), Candida n=3 (5%), Pseudomonas n=2 (8%), pneumococcus n=2 (8%), Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens and Kingella species n=1 (4%), Aspergillus n=1 (4%), NR (n=2). RHD Rheumatic heart disease; VGS Viridans group streptococci.
24 months of age (17). It is not clear why this organism causes IE in this young age group.

Approximately 50% of all IE patients and three-quarters of patients with CHD and IE in the present study had previously had cardiac surgery, and almost 50% of the cases of IE were nosocomial (19 of 40), with another two cases possibly being nosocomial because they occurred after hospital discharge but within six months of cardiac surgery. Two of the 40 cases occurred within four days of cardiac catheterization. Antibiotic prophylaxis is not recommended for diagnostic cardiac catheterization because the risk of IE is thought to be negligible, but in a previous study, seven of 73 children underwent cardiac catheterization within two months before their IE diagnosis, although six had other risk factors (including recent surgery in four cases) (11). It is possible that the risk of IE following cardiac catheterization is higher in children (especially infants) than in adults because the procedure is technically more difficult. Contrary to a previous study (12) in which 11 of 62 children with IE had normal hearts, right-sided IE and a CVC, the presence of a CVC in the absence of CHD did not appear to be an important risk factor for IE with only two cases occurring over the 19-year study period (definite IE with a tricuspid vegetation and possible IE with no vegetation seen), despite extensive use of CVCs in this large tertiary care hospital.

Surgical intervention was required in 28% of cases of IE in the current study compared with 130 of 550 (24%) in previous studies (Table 4). Indications for surgery in pediatric IE are extrapolated from adult recommendations (21), with definitive indications and ideal timing of surgery remaining controversial. The combined mortality rate of IE in all previous studies in Table 4 is 163 of 811 (20%), with the rate of 5% in the current study being comparable with that in other recent studies. Mortality is lower in adults with S aureus IE managed surgically than in those managed medically, but this could be because surgery is avoided in the most high-risk patients (24). Both deaths in the present study were due to S aureus IE, three other patients with S aureus required surgery, but another 11 cases of S aureus IE were successfully managed medically.

The definitions used for IE are not uniform across pediatric studies, although most recent studies apply the Duke criteria. Although these criteria have been shown to be more sensitive than previous criteria for the diagnosis of definite pediatric IE (25), the specificity of a diagnosis of possible IE by Duke criteria in children with CHD may be low. All children with CHD, fever and a single positive blood culture are classified as having possible IE by the Duke criteria. In a cardiac surgical centre, this includes a large number of children recovering from complex cardiac surgery — it seems likely that the vast majority of these children have contaminated blood cultures, CVC-related bacteremia or surgical site infections rather than IE, and may have a different array of pathogens than do patients with IE. In the current study, the decision was made to use the Duke criteria for definite IE, but to require stricter criteria for a diagnosis of possible IE because the primary goal was to look at causative pathogens.

CONCLUSION

Pediatric IE still occurs predominantly in the setting of CHD and is rarely associated with the presence of a CVC alone in the absence of CHD. S aureus was the predominant pathogen in many recent studies, including the current one, but a prospective population-based study would be necessary to determine whether this apparent change in etiological agents is a real phenomenon.

REFERENCES

22. S Staphylococcus aureus
Alshammary et al


