

Frequency of Infective Endocarditis Among Infants and Children With *Staphylococcus aureus* Bacteremia

Anne Marie Valente, MD*‡; Rajiv Jain, MDS; Mark Scheurer, MD||; Vance G. Fowler, Jr, MD‡¶; G. Ralph Corey, MD‡¶; A. Resai Bengur, MD#; Stephen Sanders, MD**; and Jennifer S. Li, MD*¶

ABSTRACT. *Purpose.* The prevalence of infective endocarditis (IE) among children with *Staphylococcus aureus* bacteremia (SAB) is unknown. The objective of this study was to determine prospectively the prevalence of IE among pediatric patients with SAB in a large tertiary care center.

Methods. Between July 1998 and June 2001, all children who developed SAB whose parent/guardian signed informed consent underwent echocardiography. Clinical and follow-up results were collected prospectively. Endocarditis was classified according to the modified Duke criteria.

Results. Fifty-one children developed SAB during the study interval. Definite (6 patients [11.8%]) or possible (4 patients [7.8%]) IE was present in 10 of 51 (20%) children with SAB. Most children (73%) developed bacteremia as a consequence of an infected intravascular device. Children with underlying congenital heart disease had a significantly higher prevalence of definite or possible IE, compared with those with structurally normal hearts (53% vs 3%). All patients with definite IE had multiple positive blood cultures. Mortality was high among patients with and without IE (40% vs 12%).

Conclusions. In this study, the prevalence of definite IE among children with SAB was ~12% and was frequently associated with congenital heart disease and multiple positive blood cultures. The mortality for children with SAB and definite or possible *S aureus* IE is high. *Pediatrics* 2005;115:e15–e19. URL: www.pediatrics.org/cgi/doi/10.1542/peds.2004-1152; *infective endocarditis, Staphylococcus aureus, congenital heart disease.*

ABBREVIATIONS. SAB, *Staphylococcus aureus* bacteremia; IE, infective endocarditis; TTE, transthoracic echocardiogram; TEE, transesophageal echocardiogram.

From the Departments of *Pediatrics and ‡Medicine and ¶Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina; §Department of Medicine, State University of New York, Buffalo, New York; ||Department of Pediatrics, Medical University of South Carolina, Charleston, South Carolina; #Department of Pediatrics, Rainbow Babies and Children's Hospital, Case Western Reserve University, Cleveland, Ohio; and **Departamento Medico Chirurgico di Cardiologia Pediatria, Ospedale Pediatrico Bambino Gesù, Rome, Italy.

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Address correspondence to Anne Marie Valente, MD, Division of Pediatric Cardiology, Duke University, Box 3090, Durham, NC 27710. E-mail: valen010@mc.duke.edu

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Staphylococcus aureus bacteremia (SAB) is a serious, common infection in both adult and pediatric patients. One of the most devastating complications of SAB is infective endocarditis (IE). The incidence of IE among prospectively identified adults with SAB is ~12%.^{1,2} However, the prevalence of this life-threatening infection in children with SAB is unknown. In a recent cohort of 36 prospectively identified South African children with SAB, 11% had clinically inapparent IE identified by transthoracic echocardiogram (TTE).³ However, the findings of this South African study may not be widely applicable to children cared for in tertiary medical centers in industrialized nations. Thus, the objective of this study was to determine the prevalence of IE among pediatric patients with SAB in a large tertiary care center in the United States.

MATERIALS AND METHODS

Study Design

This prospective observational cohort study was approved by the Duke University Health System's Institutional Review Board. All pediatric inpatients at Duke University Medical Center ≤18 years old with ≥1 blood culture positive for *S aureus* between July 1, 1998, and June 5, 2001, were eligible for enrollment. Written informed consent was obtained from each child's parent or legal guardian, and written assent was obtained from children ≥12 years old. Exclusion criteria included (1) inability to obtain consent from the child's parent or legal guardian (8 patients) or (2) need for sedation to obtain a TTE not otherwise indicated for clinical management (7 patients). Patients with polymicrobial bacteremia and outpatients were excluded.

Definitions

Endocarditis was defined according to the modified Duke criteria (Tables 1 and 2).⁴ Bacteremia was defined as catheter-associated if all of the following criteria were met: (1) ≥1 blood culture yielded *S aureus* while a vascular catheter was in place; (2) clinical evidence of a local infection was present (fever, inflammation at the catheter insertion site); and (3) no evidence of an alternative source was present.⁵ Hospital-acquired bacteremia was defined as a positive blood culture occurring >72 hours after admission. A follow-up blood culture was defined as a blood culture obtained 2 to 4 days after an initial positive blood culture (with antibiotic treatment).¹ Recurrence of SAB was defined as a positive blood culture for *S aureus* after treatment for an initial infection with at least 1 negative blood culture after completion of initial therapy.

Echocardiograms

All patients underwent at least 1 echocardiogram within 72 hours of the initial positive blood culture for *S aureus*. Echocardiograms obtained by the treating team for clinical management after the identification of SAB were included for study purposes. Echocardiograms were provided at no charge to all study patients with SAB in whom echocardiograms were not obtained by the

TABLE 1. The Modified Duke Criteria

Definite IE
Pathologic criteria
(1) Microorganisms demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or
(2) Pathologic lesions, vegetation, or intracardiac abscess confirmed by histologic examination showing active endocarditis
Clinical criteria
(1) 2 major criteria;
(2) 1 major criterion and 3 minor criteria; or
(3) 5 minor criteria
Possible IE
(1) 1 major criterion and 1 minor criterion; or
(2) 3 minor criteria
Rejected
(1) Firm alternate diagnosis explaining evidence of IE;
(2) Resolution of IE syndrome with antibiotic therapy for ≤ 4 days;
(3) No pathologic evidence of IE at surgery or autopsy with antibiotic therapy for ≤ 4 days; or
(4) Does not meet criteria for possible IE, as described above

treating team for clinical indications. All TTEs were performed by using Hewlett Packard Sonos 5500 machines (Hewlett Packard, Andover, MA) with 2- to 12-MHz phased-array transducers. Two-dimensional imaging from multiple tomographic planes and spectral Doppler and color-flow imaging were used in all patients. Images were recorded on 1/2-in super-VHS videotape and in digital full-screen cine loop display format (EnConcert, Andover, MA).

Findings consistent with IE included vegetation, abscess, new valvular regurgitation, and otherwise unexplained valvar dysfunction as defined previously.⁶ A vegetation (Fig 1) was defined as an irregularly shaped echogenic mass adherent to a valve or endothelial surface. Characteristics used to identify a vegetation included oscillating motion (high-frequency movement independent from associated valvar motion), mobility (exceeding and independent of the associated valve structure) and shaggy or irregular surfaces. An abscess was defined as a thickened area or mass within the myocardium or annular region, characterized by an irregular, nonhomogeneous echogenic appearance. Other unexplained valvular abnormalities consistent with IE included new valvular regurgitation at least moderate in severity or destruction or perforation of valve tissue.

TABLE 2. Definition of Terms Used in the Proposed Modified Duke Criteria

Major criteria
Blood culture positive for IE
Typical microorganisms consistent with IE from 2 separate blood cultures:
Viridians streptococci, <i>Streptococcus bovis</i> , HACEK group (<i>Haemophilus</i> species [<i>H parainfluenzae</i> , <i>H aphrophilus</i> , and <i>H paraphrophilus</i>], <i>Actinobacillus actinomycetemcomitans</i> , <i>Cardiobacterium hominis</i> , <i>Eikenella corrodens</i> , and <i>Kingella</i> species), <i>S aureus</i> ;
Community-acquired enterococci, in the absence of a primary focus; or
Microorganisms consistent with IE from persistently positive blood cultures, defined as:
At least 2 positive cultures of blood samples drawn >12 h apart; or
All of 3 or a majority of ≥ 4 separate cultures of blood (with first and last sample drawn at least 1 h apart)
Single positive blood culture for <i>Coxiella burnetii</i> or antiphase I IgG antibody titer $>1:800$
Evidence of endocardial involvement
Echocardiogram positive for IE (TEE recommended in patients with prosthetic valves, rated at least 'possible IE' by clinical criteria, or complicated IE [paravalvular abscess]; TTE as first test in other patients), defined as follows:
Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation;
Abscess; or
New partial dehiscence of prosthetic valve; or
New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)
Minor criteria
Predisposition, predisposing heart condition, or injection drug use
Fever, temperature $>38^{\circ}\text{C}$
Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway's lesions
Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, and rheumatoid factor
Microbiological evidence: positive blood culture, but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE

Outcomes

Patient outcomes were established for a minimum of 6 months after the initial positive blood culture by review of the medical records. Outcomes were defined as (1) cure (completion of therapy for SAB and no evidence of recurrent staphylococcal infection within the follow-up period); (2) recurrence (completion of therapy for SAB and clinical resolution of infection with culture-confirmed recurrent SAB [within the follow-up period]); and (3) death during the study period.

Statistical Analysis

For continuous variables, data are expressed as the mean value \pm SD unless otherwise specified. Comparisons were made between continuous variables by using the Student's *t* test. Categorical variables are expressed as a percentage. For categorical variables, comparisons between groups were made by using the χ^2 test. The Fisher's exact test and Wilcoxon rank sum were applied to nonnormally distributed data. All statistical tests were 2-tailed, and results were considered to be significant at *P* values $< .05$.

RESULTS

Clinical Characteristics of All Patients With SAB

Sixty-six children with SAB were identified in a 3-year period. Fifty one (77%) were enrolled for additional analysis after informed consent was obtained from their parent or guardian and assent was obtained, as appropriate, from the child. The clinical characteristics of these children are listed in Table 3. The gender distribution was nearly equal, and the median age of children enrolled was 16 weeks (1 week to 16 years old). Of the 51 children, 17 (34%) had congenital heart disease, including 6 with patent ductus arteriosus. Prematurity occurred in 31% of patients, and 20% had comorbid conditions.

The majority of children (73%) had an intravascular catheter in place at the time of bacteremia. Other presumed sources of SAB included postoperative mediastinitis (3 patients), urinary tract infection (1 patient), and inadvertent parenteral administration of breast milk contaminated with *S aureus* (1 patient). The organism was methicillin resistant in 15 patients

Fig 1. TTE parasternal long-axis view demonstrates a vegetation on the tricuspid valve of a patient with SAB.



TABLE 3. Clinical Characteristics of 51 Patients With SAB

	Patients With Bacteremia (n = 41)	Patients With Definite or Possible Endocarditis (n = 10)	P Value
Male gender	21 (51%)	5 (50%)	NS
Black	24 (59%)	6 (60%)	NS
White	15 (37%)	4 (40%)	NS
Age range, median	1 wk-16 y (15 mo)	3 wk-13.5 y (13 wk)	NS
Congenital heart disease	8 (20%)	9 (90%)	.02
Patent ductus arteriosus	6	0	
Ventricular septal defect	1	1	
Atrioventricular canal	0	3	
Tetralogy of Fallot	1	0	
Transposition of the great arteries	0	2	
Hypoplastic left heart syndrome	0	3	
Cleft mitral valve	0	1	
Prematurity	13 (32%)	3 (30%)	NS
Systemic disease*	10 (25%)	0	NS
Intravascular catheter	30 (73%)	7 (70%)	NS
Hospital-acquired infection	23 (56%)	9 (90%)	NS
Infection with methicillin-resistant <i>S aureus</i>	14 (34%)	2 (20%)	NS

NS indicates not significant.

*Systemic diseases included leukemia (3), immunodeficiency (2), end-stage renal disease (1), post-small bowel transplant (1), post-liver transplant (1), glycogen-storage disease (1), and epidermolysis bullosa (1).

(31%) and hospital acquired in 13 patients (87%). The most common metastatic disease was osteomyelitis, which occurred in 5 patients. Other sites of infection included pericarditis, upper extremity thrombus, and necrotizing enterocolitis.

Blood Cultures

Of the 51 patients enrolled, 50 had at least 1 follow-up blood culture; 25 patients (49%) had at least 1 positive follow-up blood culture. All 6 patients with definite IE had subsequent blood cultures positive for *S aureus*, an average of 4 positive cultures drawn 2 to 4 days after initiation of antibiotic therapy. Of the 4 patients that were classified as possibly having endocarditis, 2 of 4 had subsequent positive blood cultures.

Clinical Characteristics of IE Patients

Of the 10 patients with possible or definite endocarditis, 9 patients had hospital-acquired infection, and 8 patients had infections due to methicillin-sensitive *S aureus*. The presumed source of bacteremia was an intravascular catheter in 7 patients (70%). No association was found between the white blood cell count or temperature and risk for IE. Three patients were premature, and 9 had congenital heart disease. Of these 9 patients, 5 were diagnosed with IE within 2 weeks of surgical intervention for their congenital heart disease.

All 6 patients with definite IE met 2 major criteria as defined in Table 2. Each patient had serologic evidence of SAB and echocardiographic evidence of valvular vegetations. The 4 patients with possible IE

met 1 major criterion (serologic evidence of SAB) and 1 minor criterion (preexisting heart disease).

Echocardiography

The 41 patients with SAB had no evidence of abnormalities consistent with IE. Of 10 patients with IE, 6 had valvular vegetations identified by echocardiography: 3 had vegetations on the mitral valve, and 3 had vegetations on the tricuspid valve. Echocardiography did not reveal any new valvular regurgitation, perforation, or abscess.

Therapy and Outcome

All 10 patients with IE either completed a 42-day course of intravenous antibiotics (9 patients) or died (1 patient). One patient with endocarditis developed recurrent bacteremia after completion of therapy. The patients who did not have evidence of metastatic infection received an average of 15 days of antibiotic therapy.

Patient outcomes are reported in Table 4. The 1-year mortality rate for children with SAB was 18%. The 1-year mortality rate for patients with IE was 40%, whereas it was 12% for patients without IE. Of the 9 deaths, 4 were in children who were treated for IE; the other 5 children had multiorgan failure in the setting of chronic disease.

DISCUSSION

S aureus is a serious, common cause of bacteremia in modern medical practice. Although rates of IE in adults who develop SAB is well documented,^{1,2} its frequency in pediatric populations is less well characterized. The present investigation represents the largest prospective cohort study evaluating children with SAB using both clinical characteristics and transthoracic echocardiography. This investigation yielded several key findings.

First, 20% of the patients in this study had definite or possible IE. Previous studies of the rates of IE in children with SAB have reported varying results.^{7,8} One recent investigation demonstrated that the rate of endocarditis among 56 South African children with SAB was 11%.³ However, the generalizability of these results is limited, because patient and treatment characteristics in this developing region are likely to differ widely from current practice conditions encountered by practitioners in industrialized nations. The current investigation characterizes the nature of *S aureus* infection in children hospitalized in a large tertiary care center. One striking finding is that 9 of the 10 children with endocarditis had an

underlying congenital heart defect. SAB in children with congenital heart disease is highly associated with IE. The minor diagnostic criteria for IE include a predisposing heart condition. One of these patients, a neonate with cleft mitral valve, was only discovered at the time of echocardiogram during this study. Echocardiography is therefore a useful tool in the assessment of children with SAB, particularly neonates who may have undiagnosed congenital heart disease. Interestingly, none of the 6 neonates with an isolated patent ductus arteriosus had evidence of IE in this investigation.

Second, most patients (63%) in this study had health care-associated bacteremia. This finding has been noted in adults but not in children.⁹ Most children (73%) developed bacteremia as a consequence of an infected intravascular device, which may be especially true in premature neonates. Although the significance of IE associated with an infected intravascular catheter has been reported in adults,^{9,10} this current investigation examining the association among children did not reach statistical significance. Of the 10 patients with IE in this study, 3 were premature. There have been several reports of *S aureus* IE in premature neonates. Armstrong et al¹¹ reported 3 extremely low birth weight infants, all with percutaneous central venous catheters who developed *S aureus* IE, confirmed by echocardiography. Similarly, both of the preterm neonates in the present report with definite endocarditis also had percutaneous central venous catheters in place.

All the children in this investigation with definite IE had multiple cultures positive for *S aureus*. These findings agree with a recent prospective cohort investigation of >700 consecutive adult patients with SAB, in whom the presence of persistent bacteremia was independently associated with complicated infections.¹ These findings also support the practice of multiple blood cultures on separate days, as recommended in a recent American Heart Association scientific statement on IE in childhood.¹² Given the fact that all the children with IE in this study had clinically occult cardiac involvement, the presence of blood cultures positive after 2 to 4 days should suggest the presence of this potentially lethal complication.

Other minor diagnostic criteria for IE are much more difficult to appreciate in children, including vascular phenomena and immunologic phenomena. In fact, no children in this study had any of these clinical findings suggestive of endocarditis. This high rate of clinically occult IE emphasizes the need for echocardiographic screening among most children who develop SAB, particularly if they have congenital heart disease and/or persistently positive blood cultures.

All patients underwent transthoracic echocardiography. Children often have better transthoracic echocardiographic images than adults because of the use of higher-frequency transducers (8-12 MHz, the same as used in adult transesophageal echocardiography [TEE]), with better image resolution. The limits of

TABLE 4. Outcomes of 51 Children With SAB

	Patients With Bacteremia (N = 41), n (%)	Patients With Definite or Possible Endocarditis (N = 10), n (%)	P Value
Cure	36 (88%)	6 (60%)	NS
Recurrence	6 (15%)	1 (10%)	NS
Death	5 (12%)	4 (40%)	NS

NS indicates not significant.

resolution of using TTE in children may thus be comparable to TEE in adults.

However, transthoracic echocardiography does not detect all intracardiac vegetations, even in infants and children. It is accepted that vegetations must be >1 mm to be visualized by echocardiography. Thus, failure to detect a vegetation by TTE does not exclude IE.^{13,14} The yield rate of TTE, however, is significant when the pretest probability of IE is intermediate to high, as it is in patients with SAB. Although TEEs were not done in our cohort, the patients with negative TTEs were treated for an average of 2 weeks, which is inadequate therapy for IE. However, none had recurrence of disease during follow-up; therefore, we believe the prevalence of IE was not underestimated.

CONCLUSIONS

The prevalence of definite IE in this cohort of prospectively identified children with SAB, ~12%, was almost identical to that reported for adult patients with SAB.^{1,2} In children who met the criteria for IE, the mortality rate was 40%. Risk factors for IE in this investigation, which included the presence of congenital heart disease and/or multiple positive blood cultures, should increase suspicion for this diagnosis.

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