Increase of Fungal Endocarditis in Children

P. Tissières, E.T. Jaeggi, M. Beghetti, A. Gervaix

Abstract

Background: Infective endocarditis (IE) is a rare and feared infection that mainly occurs in patients with underlying cardiac disease or altered function of the immune system. Recent epidemiological data on both sepsis and nosocomial infections indicate a rise in gram-negative bacterial and fungal infection, particularly in patients requiring critical care support. This study sought to characterize the change in the spectrum of IE encountered in a single pediatric tertiary care center during the last 18 years, to evaluate emergence of fungal IE and to identify contributing factors.

Patients and Methods: Review of all cases of IE diagnosed between January 1986 and August 2003 at a single university children's hospital. Patients were distributed between two equal time periods and compared according to the era of IE diagnosis.

Results: In 43 patients, 44 episodes of IE were identified with most cases occurring in children with congenital or acquired heart disease. The annual number of diagnosed cases fluctuated during the study (mean 2.4 cases/year). Blood or specimen cultures were positive in 34 cases (77%) with gram-positive organisms most frequently observed (n = 20, 44.4%). Fungal IE cases (n = 9, 20%) occurred preferentially during the second period ($p < 0.03$), and were more common in children with noncardiac diseases ($p = 0.023$). Factors associated with fungal IE were the use of broad-spectrum antibiotics ($p < 0.001$) and the presence of an infected central venous catheter ($p = 0.01$). Overall mortality did not differ between the two eras.

Conclusion: The incidence of fungal IE seems to have significantly increased in more recent years. Use of broad-spectrum antibiotics for prolonged time or/and central venous catheters were identified as predisposing factors to fungal infective endocarditis.

Infection 2005; 33: 267–272
DOI 10.1007/s15010-005-4122-4

Introduction

Infective endocarditis (IE) is a feared complication of structural heart disease and, although rare in children, is associated with a significant morbidity and mortality [1]. Previous studies in children indicated that gram-positive cocci were responsible in up to 80% of IE cases, whereas fungi accounted for only 1 to 13% of infections (Table 1) [2–11]. The reported overall mortality rate ranges between 5% and 25%. Nevertheless, the spectrum of organisms may have substantially changed in recent years because of the widespread use of intravascular catheters, critical care support, improved survival of congenital heart disease patients, better diagnostic methods (microbiology, echocardiography) as well as the use and abuse of antimicrobial drugs. Recent epidemiological studies outlined an increase in fungemia during recent decades [12–14]. We aimed to analyze possible recent changes in the pattern of pediatric IE and to identify risk factors.

Patients and Methods

Patients

Retrospective case review of all episodes of IE that occurred between January 1986 and August 2003 in a tertiary university children's hospital. The diagnosis of IE was based on the modified Duke criteria using echocardiographic, microbiological, and pathological findings [15]. In order to evaluate the secular trend of the IE bacteriological pattern over the studied period, patients were divided into two equal time periods, ranging from 1986 to 1994 (group 1) and from 1995 to 2003 (group 2).

P. Tissières *(corresponding author)*
Medical ICU laboratory, Dept. of Microbiology and Molecular Medicine, University of Geneva Medical School, CMU-Rue Michel-Servet 1, 1211 Geneva 4, Switzerland; Phone (+41/22) 3795686, e-mail: Pierre.Tissieres@medecine.unige.ch
P. Tissières, E.T. Jaeggi, M. Beghetti
Cardiology Unit, Dept. of Pediatrics, University Children's Hospital, Geneva, Switzerland
A. Gervaix
Infectious Disease Unit, Dept. of Pediatrics, University Children's Hospital, Geneva, Switzerland

Received: October 7, 2004 • Revision accepted: April 13, 2005

Definition

A catheter-borne IE was considered if a vegetation was identified echocardiographically on the tip of a central venous catheter and if more than 103 colony-forming units per centimeter of an isolated microorganism were quantified in the culture of the catheter tip [16].

Microbiology

Daily, one to two blood samples were systematically drawn in all cases with suspected IE and usually cultured for 21 days under aerobic and anaerobic conditions. All microorganisms were identified using standardized procedures at the hospital's central laboratory of bacteriology. The samples were distributed into a Septi-Chek Release bottle (Becton Dickinson, Cockeysville, MD) and an Oxoid Signal bottle (Oxoid, Basingstoke, UK). Whenever fungemia was suspected, the inoculation of an Isolator 10/1.5 tube (Wampole Laboratories, Cranbury, NJ) based on lysis centrifugation was performed. With the introduction of an automated fluorometric BACTEC 9000 system in the clinical microbiology bacteriology laboratory (August 1994), the Septi-Chek Release and Signal vials were replaced by the BACTEC Plus aerobic/F, BACTEC PEDS Plus /F and the Lytic anaerobic/F vials (Becton Dickinson, Sparks, MD). The Isolator was replaced when the BACTEC Myco/F Lytic medium became available (November 1997). Yeasts growing in all cultures were identified with API C32 (BioMérieux, Lyon, France) in conjunction with microscopic morphology of the fungi subcultured on rice agar. In one case of *Bartonella quintana* IE, broad-range PCR amplification was performed on excised mitral valvular tissue, sequenced and compared with sequences of bacterial 16S ribosomal RNA genes deposited in Genebank and the European Molecular Biology Laboratory database [17, 18].

Echocardiography

All children underwent complete transthoracic 2-dimensional and Doppler echocardiographic studies at diagnosis and follow-up using Vingmed Diasonics, CFM 700 or System Five ultrasound systems with 5 to 7 MHz phased-array transducers. Because of inconclusive transthoracic echocardiographic exam, nine patients underwent additional transesophageal echocardiography with a 5 MHz multiplane probe. Unlike in adults, transthoracic and transesophageal echocardiographies are considered equally accurate for the diagnosis of IE in children, in particular for the detection of vegetations [19]. All ultrasound studies were videotaped and available for off-line analyses.

Statistics

To determine differences between groups, nonparametric Mann-Whitney U test and a two-tailed Fisher's exact test were performed. A p-value < 0.05 was considered to be significant.

Table 1
Pediatric series on infectious endocarditis.

	Patients' age (years)	Gram positive (%)	Gram negative (%)	HACEK group (%)	Fungi (%)	Culture negative (%)
Johnson et al. [2] (1953–1972) (N = 149)	0.1–23.1	20	1	–	–	79
Van Hare et al. [3] (1972–1982) (N = 42)	0–20	91	2	5	–	2
Fukushige et al. [4] (1971–1990) (N = 29)	0.8–17.3	83	–	–	–	17
Awadallah et al. [5] (1970–1990) (N = 48)	0.8–32	56	na	na	6	11
Martin et al. [6] (1958–1992) (N = 76)	0.08–18	86	2	5	–	7
Saiman et al. [7] (1977–1992) (N = 62)	0.09–19	72	11	–	10	7
Del Pont et al. [8] (1978–1994) (N = 43)	0.08–22	74	–	–	13	13
Bitar et al. [9] (1977–1995) (N = 41)	3–18	66	10	–	–	24
Stockheim et al. [10] (1978–1996) (N = 111)	0.02–20	75	11	5	4	5
Sadiq et al. [11] (1997–2000) (N = 45)	0.3–16	34	11	–	2	53
Geneva Children's Hospital (1986–2003) (N = 44)	0.2–18	44.4	6.7	6.7	20	22.2

HACEK group: *Hemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella*, *Kingella*; na: not available, HACEK group and gram negative: 27%

Results

44 IE episodes were diagnosed in 43 children (23 girls) aged between 1 week and 18 years (median: 7 years). Most children originated from northern (n = 20) or sub-Saharan (n = 13) Africa, while ten children were from continental Europe. 40 patients (91%) with underlying congenital or acquired heart disease were referred for cardiac surgery (including all children originating from the African continent). Among these, 24 (60%) occurred in the postoperative period, including 15 cases within the first 2 weeks following surgery. Two IE cases occurred in premature newborns, and the remaining two in children after liver or kidney transplantation. Among those with cardiac disease, seven (17.5%) had acquired valvular disease secondary to rheumatic fever, 21 (52.5%) had cyanotic and 12 (30%) acyanotic congenital heart disease.

Blood (19 cases with ≥ 2 positive blood cultures, and five cases with one positive blood cultures) or perioperative specimen cultures and serological tests were positive in 34 (77%) of the 44 IE episodes. The most frequently observed microorganisms were gram-positive organisms (n = 20 [44.4% of cases]: *Staphylococcus aureus* [n = 7], *Staphylococcus epidermidis* [n = 2], and *Staphylococcus lugdunensis, Streptococcus mitis* [n = 2], *Streptococcus pyogenes, Streptococcus pneumoniae, Streptococcus milleri, Streptococcus sanguis, Enterococcus faecalis, Corynebacterium diphtheriae, Propionibacterium acnes, Actinomycetes odontolyticus*) and fungi (n = 9 [20%]: *Candida albicans* [n = 6], *Candida guillermondi* [n = 2], and *Hansenula anomala*). Less common were microorganisms from the HACEK group (n = 3 [6.7%]: *Haemophilus paraprophilus, Haemophilus influenzae, Haemophilus aphrophilus*) and gram-negative (n = 3 [6.7%]: *Pseudomonas aeruginosa*, *Bartonella quintana, Salmonella typhii*), while *Coxiella burnetti* caused IE in one case. Ten cases (22.2%) had culture-negative endocarditis. Polymicrobial IE was observed in one case that developed a brain abscess secondary to systemic septic emboli. The primary site involvement was equally found in right- (n = 19) and left-sided cardiac cavities (n = 20). Four cases had multiple intracardiac infective locus at diagnosis. Native valves were primarily involved in 26 cases, including two cases with mitral and aortic valve IE. Secondary IE spreading occurred in 18 cases (41%), and included eight Dacron patches, a mechanical valve and four cases with symptomatic septic embolizations to the brain. Among the 19 patients with a central venous catheter, seven (36.8%) had a catheter-borne IE. The catheters were in place between 2 and 42 days (median: 12 days) with a trend that did not reach statistical significance in duration between catheter-borne IE (21.5 ± 16.6 days) and those that were not infected (13.5 ± 11.5 days). In 21 cases (48%), broad antibiotic (BA) therapy had been given during the 8.4 ± 14 days prior to IE diagnosis. The use of BA, mainly aminopenicillins, with or without aminoglycosides, and third-generation cephalosporins was based in most cases on clinical symptoms of fever and elevated inflammatory biological parameters suggesting bacterial infection. Four patients with negative blood culture IE received BA. Incidence of IE during the last 18 years (Figure 1) revealed a fluctuating number of yearly diagnosed cases (mean 2.4 per year), with no significant difference in the occurrence of gram-positive, gram-negative, and blood culture-negative IE (Figure 2) during the two study eras.

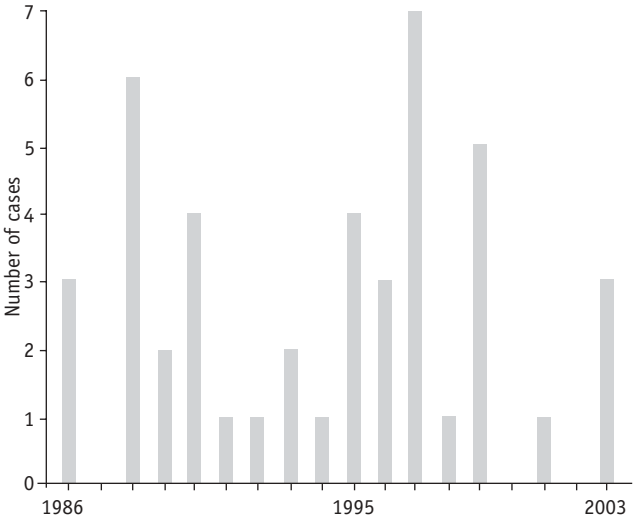

Figure 1. Infective endocarditis yearly occurrence.

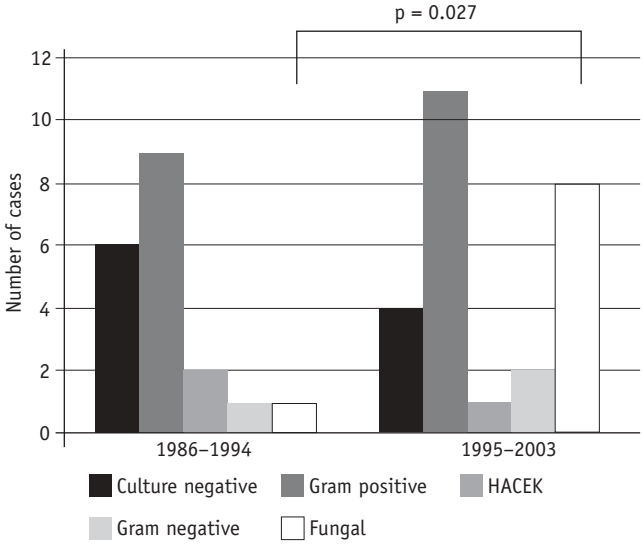

Figure 2. Bacteriological pattern of infective endocarditis over two 9-year periods.

Fungal IE was found in nine cases (20%) and most (n = 8) occurred within the second era ($p < 0.03$). The modification of the bacteriological techniques that occurred in 1997 did not influence ($p = 0.081$) the increase in fungal IE diagnosis. Out of the eight fungal IE cases diagnosed

Table 2
Difference between fungal and infective endocarditis of other causes.

	Fungal IE (n = 9)	IE of other causes (n = 34)	P-value
Age (years ± SD)	6.65 ± 6.35	8.35 ± 4.89	NS
Female gender (number [%])	5 (55.5)	18 (53)	NS
European origin (number [%])	3 (33)	7 (20.5)	NS
Cyanotic CHD (number [%])	6 (66.7)	16 (47)	NS
Noncardiac disease[a] (number [%])	3 (33.3)	1 (2.8)	0.023
Postoperative IE (number [%])	4 (44.4)	17 (50)	NS
Infected CVC (number [%])	5 (55.5)	2 (5.9)	0.01
Duration of catheter prior to IE diagnosis (days ± SD)	20 ± 14.4	13.8 ± 13	NS
BA before IE diagnosis (number [%])	9 (100)	12 (35.3)	< 0.001
Duration of BA treatment before IE diagnosis (days ± SD)	16.1 ± 21	5.6 ± 9.8	NS
Infected implantable materials/total (number)	4/6	6/11	NS
Follow-up (years ± SD)	2.38 ± 1.25	4.47 ± 3.78	NS
Overall survival (%)	55.6	85.7	NS

SD: standard deviation; NS: nonsignificant ; IE: infective endocarditis; BA: broad-spectrum antibiotics; CHD: congenital heart disease; CVC: central venous catheter; [a] noncardiac disease: post-transplantation and prematurity

during the second period, five occurred after November 1997. In addition, reported experience comparing both the BACTEC MYCO/F Lytic bottle and the Isolator system did not show improvement in fungal detection [20]. Characteristics of patients with and without fungal IE are compared in Table 2. On univariate analysis, risk factors contributing to fungal IE were: prior administration of BA (9/9 cases; $p < 0.001$) and the presence of an infected central venous catheter at the time of IE diagnosis (5/9 cases; $p = 0.01$). The four patients without underlying heart disease (two with solid organ transplant and the two prematurely born infants) were prone to fungal IE (three of totally nine cases; $p = 0.023$). Although a trend was observed, there was no significant difference between fungal IE and IE of other causes in the duration of both BA therapy (16.1 ± 21 vs 5.6 ± 9.8 days; p = NS), or of central venous catheter (20 ± 14.4 vs 13.8 ± 13 days; p = NS).

The median follow-up after diagnosis of IE was 7 years (range: 0.4–19 years). Survival was lowest with fungal (56%) and gram-negative (67%) endocarditis. The outcome of children with gram-positive, HACEK or Q fever, and blood culture-negative IE was significantly better, with survival rates of 88%, 100% and 80%, respectively. The mortality rate did not differ between the two study eras (25% vs 16.7%).

Discussion

The spectrum of organisms identified in pediatric IE has been rather uniform during many decades (Table 1). Gram-positive bacteria were the main cause of IE, whereas fungal infections were infrequently described (2–13%). In our institution, the bacteriological spectrum has evolved during the 18-year study period towards more fungal infections, albeit the overall incidence of IE did not change. Gram-positive microorganisms remain the principal cause of IE. Still, there was a surprisingly high number of culture-negative IE throughout the study period. However, although *Martin* et al. [6] showed that 80% of culture-negative IE had previous BA treatment, our data did not demonstrate this association. Only four (40%) of our patients with negative culture IE had prior BA. On the other hand, BA was given in 17 (50%) of the children with bacteriologically identified IE. Although all operated children did receive intravenous cephazolin prophylaxis, culture-negative IE prevalence was similar in immunocompromised and premature children. Whether the increase in fungal IE diagnosis is solely related to a shift from negative blood culture and gram-negative infections is not elicited by our data.

The observed increase of fungal IE in the second era goes along with the reported increase of fungal sepsis in both adults and children [12, 13, 21, 22]. Although the incidence of invasive fungemia seems to have stabilized in recent years, a striking increase ranging from 180- to 620-fold was observed between the early 1980s and the 1990s in the pediatric and neonatal population [23, 24]. Similar to our data, two other pediatric series described a worrying prevalence (10–13%) of fungal IE, but little data about these children were available [7, 8].

Unrelated to the operative status, the use of BA was found to be an important risk factor for fungal IE. The use of BA was based in most cases on clinical symptoms of fever and elevated inflammatory biological parameters (such as C-reactive protein), suggesting bacterial infection. However, patients who underwent cardiopulmonary bypass commonly have elevated C-reactive protein and fever in the early postoperative course, impeding the decision to introduce BA. Recently, serum procalcitonin has shown promising results in identifying bacterial infection after cardiac surgery, and may help in a more rational use of antibiotics after cardiac surgery, as well as in the immune-deficient, severely ill child [25, 26]. A second identified risk factor for fungal IE was the presence of an infected central venous catheter. In a third of the cases, infection of the central venous catheter could be identified before infective endocarditis was diagnosed. Other predisposing factors for fungemia such as neutropenia, mechanical ventilation, parenteral nutrition, steroids as well as chemotherapy were extensively reported [27]. In addition, pediatric experiences reported a prolonged length of stay of more than 7 days

in the ICU, and low birthweight as predisposing factors to fungemia [28, 29]. Our data clearly demonstrated the relation between some predisposing factors and the development of fungal IE, suggesting that early indices of suspicion for fungal IE should be considered especially if predisposing factors are met. Although no definite recommendations exist for fungal screening in pediatric non-immunocompromised critically ill children, calculation of a fungal colonization index based on multi-site screening may help to diagnose invasive fungemia if predisposing factors are met [30].

The mortality rate in previously published series on pediatric IE ranges between 3% and 25% [2–11]. We encountered an overall mortality reaching 21%, with no difference between the two study eras. In our cohort, the elevated mortality may be influenced by the increased number of children with cardiac disease and the associated mortality.

Besides the retrospective design of this study, the lack of information on the volume of blood drawn is an important shortcoming of this study as it is known that a sufficient volume is critical for bacterial isolation [31].

In conclusion, although limited by a relatively small series and a referral bias related to the large cohort of cardiac patients, our data suggest a rise in the prevalence of fungal IE, which is associated with the use of BA and central venous catheters. Fungal IE has a high risk of mortality (44%); early diagnosis and treatment might be crucial for the outcome of affected children.

Acknowledgement

The authors thank Peter Rohner, M.D., from the Clinical Microbiology Laboratory of the University Hospitals of Geneva, for providing technical data regarding former and current microbiology techniques.

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