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Incidence of infective endocarditis and its thromboembolic complications in a pediatric population over 30 years

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ABSTRACT

Background: Pediatric infective endocarditis (IE) has been associated with high morbidity and mortality, mostly related to thromboembolic complications (TEC). The objective of our study was to describe the experience in children with IE and to review the changes over a thirty-year period, regarding origin of IE, incidence of vegetations, TEC and their respective morbidity and mortality rates.

Methods: A retrospective chart review of children aged 0–18 years with IE defined by the Duke Criteria and admitted to The Hospital for Sick Children, was conducted. Data were divided into three periods (P); P1 (1979–1988); P2 (1989–1998); and P3 (1999–2008).

Results: The study included 113 patients, median age 7 yrs.; females: 46 (41%), congenital heart defects 95 (84%), comparable in all periods. Overall, cardiac vegetations were found in 68/113 patients (60%); large vegetations (≥1 cm) in 32 patients (28%). Fourty-five (45/133 [40%]) TEC were documented, 22 patients (20%) developed cerebrovascular events (CVE) and 23 patients (20%) had non-CVE. Patients diagnosed during P3 were older, had more vegetations ($p < 0.05$), and a higher incidence of community acquired-IE ($p < 0.05$). Overall, mortality was 15%, comparable in all periods. Significant risk factors for mortality were vegetations (HR 6.44; 95% CI: 2.07–20.01, $p = 0.002$) and heart failure (HR 28.39; 95% CI: 10.49–76.85, $p < 0.001$).

Conclusions: Over the study period, we report a growing incidence of community acquired pediatric IE in older children accompanied by an increasing rate of TEC. Heart failure and vegetations were associated with an increased mortality. These preliminary data need to be confirmed by prospective data.

1. Introduction

Infective endocarditis (IE) is a rare but serious condition in children with an incidence estimated between 0.34 and 0.64 cases per 100,000 per year [1]. To date, the diagnosis of pediatric IE is still challenging and frequently delayed, with a reported mortality in children ranging from 4 to 25% [2,3]. According to adult data, systemic embolism occurs in 13 to 50% of patients with IE. Thromboembolic complications (TEC) into major arteries and organs significantly contribute to disease morbidity [4–6]. Cerebro-vascular events (CVE), including acute ischemic strokes (AIS), are reported in 20 to 40% of patients with IE [7–9]. For children, a small retrospective series reported 6% IE related AIS [10].

Location and size of intracardiac vegetations have been identified as risk factors in various studies for cardioembolic AIS in adults [11]. Initiation of prompt antimicrobial treatment is considered the mainstay in both the treatment of IE and in the prevention of thrombotic complications, including AIS [12]. Despite the importance of thrombotic events in patients with IE, the use of anticoagulation and antiplatelet therapy is highly controversial. On the one hand, an inverse dose-dependent response to acetylsalicylic acid on vegetation growth, microbial proliferation and renal embolization has been described for experimental *Staphylococcus aureus* (*S. aureus*)-induced IE [13]. On the other hand, uncertainty about the appropriateness of such treatment modalities continues, as reflected by the most recent pediatric and adult antithrombotic and IE guidelines [12,14,15]. Currently there is no evidence to support anticoagulation or antiplatelet therapy for patients with IE [16].

The objective of the current study was to review a single-center experience with IE in children and to describe changes over 30 years,

Abbreviations: IE, infective endocarditis; TEC, thromboembolic complication; P1, 2, 3, periods 1, 2 and 3; (Non)-CVE, (non)-cerebrovascular events; CA-IE, community acquired-infective endocarditis; AIS, arterial-ischemic stroke; CHD, congenital heart disease; PE, pulmonary embolism; TTE, transthoracic echocardiography; TEE, transesophageal echocardiography; BC, blood culture.

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regarding origin of IE, incidence of vegetations and TEC. In addition, we aimed to describe risk factors for IE-related TEC and mortality.

2. Methods

A retrospective chart review including only pediatric patients with definite IE, as per modified Duke Criteria, was conducted [17] In patients without vegetations, IE diagnosis was made according to positive blood culture (BC) or to minor criteria including prolonged fever, CHD, new regurgitation murmur, and vascular or embolic phenomena. Thromboembolic complications were included if confirmed radiologically and occurred after confirmation of IE as per the modified Duke Criteria for vascular complications [17].

Consecutive patients diagnosed with IE, admitted to The Hospital for Sick Children, Toronto (Canada) between January 1978 and January 2008 were eligible. Patients whose admitting and/or discharge diagnoses included IE were retrieved from either the Cardiology or the Thrombosis service database. Permission to use and analyze the data was obtained from the local Research Ethics Board of The Hospital for Sick Children, Toronto (Canada). Demographic data obtained included: age, gender, underlying disease, congenital heart (CHD) type (cyanotic or acyanotic), previous cardiac surgery, cardiac interventions or previous IE as well as non-cardiac interventions prior to IE diagnosis (e.g. other surgery, vaccinations, dental procedures). A standardized case report form was completed for each patient to maximize data collection consistency and quality.

2.1. Definitions

Nosocomial infection consisted of any infection, occurring ≥72 h after hospital admission [18]. Postoperative IE was defined as IE diagnosed within 6 months after surgery [19].

Thromboembolic complications (TEC) included cerebrovascular events (CVE) or non-CVE, as follows: a) CVE, including AIS, mycotic aneurysms or hemorrhages; and b) non-CVE, defined as radiologically-confirmed thromboembolism outside the central nervous system. The indication to perform radiological investigation was the clinical suspicion of a TEC. Major bleeding events secondary to either antiplatelet or anticoagulant use were defined as per internationally accepted criteria [20].

Surgical intervention encompassed any surgery related to IE: early surgery comprised surgery up to three days after diagnosis of IE.

Heart failure was defined and confirmed by cardiology staff physician; this information was confirmed in the consultation notes. Due to the retrospective study design, mortality included only perioperative deaths or endocarditis-related mortality up to 30 days after the diagnosis of IE was confirmed.

2.2. Statistical methods

To determine trends in childhood IE over the surveyed 30 years, the total observation time was divided into equal time periods of 10 years, each: period 1 (P1; 1979–1988), period 2 (P2; 1989–1998) and period 3 (P3; 1999–2008).

Descriptive statistics including percentages and medians were calculated. Mann–Whitney-U-test was used for comparison between groups with continuous variables and Chi-square-test for comparison of categorical variables. Univariable and stepwise multivariable logistic regression were conducted for exploratory analysis of risk factors associated with TEC and mortality. Variables showing a trend for an association with the dependent variable (p value ≤ 0.1) in the univariable analysis were included in the multivariable analysis. Significance level was set up at alpha <0.5.

3. Results

3.1. Demographic data

The initial cohort using the diagnostic code for IE comprised 152 patients. Thirty nine patients were excluded for the following reasons: i) no definite IE according to Duke criteria (n = 30), ii) unavailable or incomplete data (n = 7), iii) postmortem diagnosis of IE (n = 2). The final study cohort consisted of 113 patients, aged 1 day to 18 yrs., with 41 patients (36%) aged ≤3 yrs. The median age was 7.0 yrs., 46 patients (41%) were females. Underlying CHD was present in 95/113 patients (84%), acyanotic CHD in 61/113 patients (54%) and cyanotic CHD in 34/113 children (30%).

3.2. Characteristics of the surveyed periods

Table 1 shows characteristics of patients in the surveyed time periods. Period 1 (P1) comprised 31 (27%) patients, P2: 47 (42%) and P3: 35 (31%) children. Median age at diagnosis was significantly ($p < 0.001$) higher in P3 (12.3 years) compared to P1 (3.0 years) and P2 (4.0 years, $p < 0.001$). In P3, a significantly higher incidence of community-acquired IE (77% [P3] vs. 48% [P1] vs. 57% [P2], $p = 0.01$) existed compared to the prior two study decades. Additionally, patients in P3 had higher incidences of vegetations (71% [P3] vs. 45% [P1] vs. 62% [P2], $p = 0.01$) with comparable CVE, but increasing non-CVE (26% [P3] vs. 13% [P1], $p = 0.43$).

3.3. Thromboembolic complications

Fourty-five thrombotic events (45/113 [40%]) were documented. Cerebrovascular events (CVE) were documented in 22/113 children (19%). An acute ischemic stroke was diagnosed 18/113 patients (16%) and cerebral mycotic aneurysms in 4/113 children (3%). Non-CVE was present in 23/113 cases (20%). Among those with non-CVE, 9/113 children (8%) developed pulmonary embolism, 6 (5%) had kidney infarcts, 5 (4%) had splenic infarcts, and 3 (3%) had osteomyelitis complicated by bone abscess formation. Overall, children above 3 years had longer (median 17 days) fever periods with prolonged clinical courses compared to patients younger than 3 years (median 12 days, n.s.). An exploratory analysis was conducted to identify risk factors associated with TEC. The logistic regression found age above 3 years to be significantly associated with TEC, including CVE and non-CVE ($p = 0.01$). Congenital heart diseases ($p = 0.33$), causative microorganisms ($p = 0.95$) and heart failure ($p = 0.51$) were not associated with TEC.

3.4. Vegetations

Vegetations were identified by either transthoracic (TTE) or transesophageal echocardiography (TEE) in 68/113 cases (60%). Location of vegetations is given in Table 1. During P1, TEE was not done whereas in P2 15/29 patients (52%) with vegetations had TEE with 13/15 (87%) positive exams for vegetations (vegetation only seen in TEE [n = 1], lesion only visible in TTE [n = 1]). During P3 17/25 children (68%) who had developed vegetations underwent TEE (vegetation only seen by TEE [n = 2]). Overall, from 68 patients with vegetations, 45/68 (66%) developed TEC. Whereas of the 42 patients without vegetations 12/42 (29%) developed TEC (8 CVE 6 non-CVE, 2 both; $p < 0.001$). In another three patients there was no information regarding vegetation. In 32/113 children (27%) large (≥1 cm) vegetations were documented and of these, 18 children (18/32 [56%]) developed TEC.

3.5. Causative microorganisms

The causative microorganism was identified by BC in 105/113 children (93%). *Staphylococcus aureus* was found to be the causative microorganism in 43 cases (38%). The remaining patients had positive BC for *Streptococcus viridans* (29 [26%]), *Staphylococcus epidermidis* (14 [12%]), *Streptococcus pneumoniae* (3 [3%]), *Candida albicans* (2 [2%]), combined organisms (6 [5%]) and miscellaneous (8 [7%]) microorganisms (*Haemophilus influenza* [1], *Enterococcus* [2], *Actinobacillus* sp. [1], *Pseudomonas aeruginosa* [2], *Pasteurella* sp. [1], and *Streptococcus abiotrophia* [1]). Eight patients (7%) had BC-negative endocarditis. Of these, 5 children were diagnosed by a biopsy after surgery and 3 children by clinical criteria according to the Duke Criteria. During the entire study period, an increasing rate of *S. viridans* and decreasing rate of *S. aureus* as the causing organisms were found.

3.6. Origin of IE and antibiotic prophylaxis

Overall, community acquired-IE was seen in 69/113 (61%) and nosocomial IE in 44/113 cases (39%) with comparable proportions of CHD over time. Children with community acquired-IE were significantly older than in the nosocomial group (median age 10.8 yrs. vs. 0.7 yrs., $p < 0.001$), had more vegetations ($p = 0.016$) and a higher incidence of IE-related surgical interventions ($p = 0.009$). *S. viridans* was the dominant causative microorganism in CA-IE ($p < 0.001$) compared with IE in the nosocomial group (Table 2).

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