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Incidence, predictors and outcomes of infective endocarditis in a contemporary adult congenital heart disease population

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ABSTRACT

Background: The prevalence of congenital heart disease (CHD) in the adult population is steadily increasing. A substrate of prosthetic material and residual lesions, constantly evolving as surgical techniques change over time, predispose these patients to the potentially devastating complication of infective endocarditis (IE).
Methods: We retrospectively reviewed 2935 patients in our adult CHD database for all cases of endocarditis between 1991 and 2016. Incidence, clinical course and predictors of outcomes were analysed.
Results: We document 74 episodes in 62 patients, with an incidence of 0.9 cases/1000 patient years (py). IE was more common in complex CHD (1.4 cases/1000 py) and ventricular septal defects (VSDs) (1.9 cases/1000 py). Prosthetic material was involved in 47% and left-sided infection predominated (66%). The incidence in bicuspid aortic valves post aortic valve replacement (AVR) was significantly higher than in unoperated valves, being 1.8 and 1.1 cases/1000 patient years respectively. *Streptococcus* was the most frequently implicated causative organism (37%). Emboli occurred in 34% of cases with a cerebral predilection. 46% of patients required surgery during the admission for IE, most frequently to replace a severely regurgitant bicuspid aortic valve. Early endocarditis-related mortality was 15%, associated with cerebral emboli and acute renal failure.
Conclusions: In a contemporary adult CHD cohort, those with complex underlying lesions, VSDs or an AVR were at higher risk for IE. Mortality remains substantial and is more likely in patients with cerebral emboli and/or acute renal failure.

1. Introduction

The survival of patients with congenital heart disease (CHD) has markedly improved over the last several decades with advances in their paediatric medical care [1]. This brings the unique challenge of caring for more surviving adults than children with CHD, including severe forms [2]. The presence of either prosthetic material or residual uncorrected lesions creates a high-risk substrate for infective endocarditis (IE), a potentially devastating complication [3,4]. The majority of IE literature describes acquired heart disease [5], paediatric CHD [4] or adult CHD (ACHD) cohorts from the 1980s to 1990s [6]. This may not reflect current patterns of disease. Only recently has attention been turned to population based incidence in ACHD, with a rate clearly exceeding that of the general population [7].

The clinical course of IE once diagnosed is significantly morbid, with estimated endocarditis-related mortality of 2–24% [3,7–9]. This emphasises the importance of predicting those at higher risk for developing IE, particularly in the face of changing antibiotic prophylaxis guidelines [10]. Unrepaired ventricular septal defects (VSDs), bicuspid aortic valves (BAVs), complex lesions and prosthetic material (particularly valve-containing) have all been implicated as high risk situations [4,6,7,9,11].

We used the ACHD database in our quaternary referral centre to examine the incidence of IE in those ≥16 years of age. Clinical course, outcomes and predictors of mortality were analysed in this relatively contemporary cohort.

2. Methods

A retrospective single centre review was performed at a quaternary ACHD referral centre in Sydney, Australia. This is the only ACHD centre state-wide with a catchment of 6–7 million people. 2935 patients aged ≥16 years old and seen at least once since January 2000, were included. All definite episodes of endocarditis by Duke's criteria [12] occurring over the age of 16 were analysed; there were 74 episodes in 62 patients. Acquired cardiac lesions or small atrial septal defect (ASD)/patent foramen ovale were excluded. Patient years followed was calculated by multiplying the number of patients by the total years between their 16th birthday (age at referral to our ACHD centre) and last known vital status. Last known vital status was taken as either time of death, or if alive, the date of our last National Death Index Survey (31st December 2014), or last follow up, whichever occurred later. Incidence of IE overall and by Bethesda level of complexity for underlying CHD

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[13] was calculated by dividing the number of IE episodes by total patient years followed for each group, then multiplying by 1000 (expressed in cases per 1000 patient years).

The following clinical information was analysed: age at diagnosis, gender, underlying congenital defect, cyanotic status, prior cardiac surgeries, symptom type and duration, portals of infection, organism, echocardiographic findings, antibiotic choice and duration, need and indication for surgery, complications and outcomes. Cardiac surgery within 6 months of presentation was considered a predisposing factor. Prosthetic associated IE included either definite or probable diagnoses, based on imaging and clinical assessment. Relapsed IE was defined as a repeat episode within 6 months with the same causative organism; recurrent episodes occurred either later than 6 months or due to a different organism. Acute renal failure was defined as either an increase in serum creatinine of >200% or an increase by >44 μmol/L (0.5 mg/dL) to ≥350 μmol/L (4 mg/dL) [14]. Emergency surgery was defined as surgery for a life threatening indication or hemodynamic instability within 24 h of admission. Early endocarditis related mortality was defined as within 3 months of admission.

Statistical analysis was performed using Statistical Package for Social Services V.22.0 (SPSS, Chicago Illinois). Continuous variables are presented as mean +/− standard deviation (SD) or median with range. Student's unpaired *t*-test and Wilcoxon rank-sum test were used for comparison of continuous variables. Categorical variables are presented as frequencies and percentages. Comparison of categorical variables was performed using Chi squared or Fischer's exact test. Univariate and multivariate analyses to identify predictors of events were completed using logistic regression analysis. For the purposes of predictive analysis, the most recent episode in those who had recurrent IE was used. A two-tailed value of $p < 0.05$ was considered statistically significant. Incidence rates were calculated with Poisson regression and are presented with confidence intervals (CI).

3. Results

3.1. Incidence by complexity of congenital heart disease

In 2935 patients followed for 85,276 patient years, IE occurred in 62 patients (2.1%). 74 episodes of IE corresponded to an overall incidence of 0.9 cases/1000 patient years (py) (95% CI 0.7–1.1). Three patients had recurrent IE twice and 6 had a single recurrent episode; none had a relapsed episode. Average age at diagnosis was 37 years (16–68, SD 13) with a male predominance (76%, $n = 56$). Follow up post IE averaged 5.4 years (SD 5.2). Table 1 shows incidence of IE by complexity of underlying CHD. IE was more common in complex CHD (1.4 cases/1000 py, 95% CI 0.8–2.4) and VSDs (1.9, 95% CI 0.9–3.4). BAVs contributed 614 patients to the simple CHD group with a higher incidence of IE in those post aortic valve replacement (AVR) (10/135, 1.8, 95% CI 0.9–3.4) compared to those without (23/483, 1.1, 95% CI 0.7–1.6). No cases were observed in patent ductus arteriosus (PDA) and a low rate of 0.3 (95% CI 0.1–0.8) was seen for atrial septal defects (ASDs). Underlying lesions in the moderate complexity category included 4 coarctation patients, 4 tetralogy of fallot patients, 3 with atrioventricular septal defect and 2 with VSD. The complex category included 10 transposition of the great arteries (+/− VSD +/− pulmonary stenosis or atresia) patients, as well as 4 with functionally univentricular hearts.

3.2. Baseline patient characteristics and presentation

Corrective surgery had been performed in 36 (49%), palliative surgery in 4(5%) and no intervention in 34 (46%). 5 cases occurred in cyanotic patients (7%). The average duration of symptom onset to diagnosis was 27 days (1–210, SD 42). Fever was the most common symptom (84%, $n = 61$), followed by malaise (23%, $n = 17$) and dyspnoea (22%, $n = 16$). The range of clinical presentations was broad and included arthralgias, gastrointestinal and neurological symptoms in 18%, 8% and 8% respectively. Predisposing factors were identified in 18 (24%); cardiac surgery within 6 months in 10, intravenous drug use in 6, recent dental intervention in 2, dog bite in 1 and brucella acquired from unpasteurised milk in 1.

Clinical features at time of diagnosis are seen in Table 2. Echocardiography was positive for vegetations in 61 cases (82%), commonly revealing left sided infection (66%, $n = 49$). 35 cases (47%) were either confirmed or suspected to involve prosthetic material. Bearing in mind that vegetations were commonly seen at multiple prosthetic sites in the one patient, involved sites included: 14 AVRs (7 tissue, 7 mechanical), 5 prosthetic aortic roots, 6 sub-pulmonary ventricle to pulmonary artery conduits, 2 Melody pulmonary valves, 2 tricuspid valve replacements, 3 atrial baffles, 3 VSD patches and 11 device leads. The average time post cardiac surgery to development of IE in these cases was 9.5 years (0.2–35, SD 11.0). Furthermore recurrent IE was significantly more likely in patients with IE related to the presence of prosthetic material (OR 5.9, 95% CI 1.4–25.5, $p = 0.017$).

In blood culture positive episodes (91%), the most common organism isolated was *Streptococcus* (37%) followed by *Staphylococcus aureus* (28%). Unusual organisms such as brucella, bartonella, erysipelothrix rusiopathae and *Corynebacterium urealyticum* were documented in single cases.

3.3. Complications and outcomes

Table 3 highlights complications and outcomes of endocarditis presentations. Emboli were seen in 34%, most commonly cerebral. Cerebral CT scanning was performed in the presence of neurological signs or symptoms, or at the clinician's discretion if the patient was determined to have a high embolic risk or proven emboli elsewhere. An embolic event was more likely in the setting of staphylococcal bacteraemia (48% versus 18%, $p = 0.007$) and when vegetation size was ≥10 mm (56% versus 24%, $p = 0.007$). The only case of cerebral abscess occurred in a cyanotic patient. Intravenous antibiotics were prescribed for an average of 5.7 weeks (SD 2.0), with 12 (16%) receiving an additional oral course. Regimes included benzylpenicillin and gentamicin in 26%, flucloxacillin in 23%, vancomycin/gentamicin combinations in 15%, ceftriaxone in 12%, benzylpenicillin alone in 9% and vancomycin alone in 8%. Surgery was performed within 3 months of index presentation in 34 (46%), an average duration of 54 days post diagnosis. In 16 cases (22%) this was a single valve replacement, double valve in 5 (7%), aortic

Table 1
Incidence of infective endocarditis by complexity of congenital disease.

Lesion severity	All	% of total population	IE episodes	% of IE cohort	Incidence (per 1000/patient years) (95% CI)
Simple	1412	48	45	61	0.9 (0.6–1.2)
Moderate	960	33	15	20	0.7 (0.4–1.1)
Complex	520	18	14	19	1.4 (0.8–2.4)
Unclassified	42	1	0	0	0.0

IE = infective endocarditis.

Table 2
Baseline characteristics at time of diagnosis.

Characteristic	Number	%
Cyanotic	5	7
Recurrent episode	16	22
Echo positive (TTE or TEE)	61	82
TEE performed	50	69
Location		
Left sided	44	59
Right sided	19	26
Both left and right sided	5	7
Size vegetation		
<10 mm	28	38
≥10 mm	26	36
Unknown size	20	26
Prosthetic	35	47
Blood culture positive	67	91
Organism		
Streptococcus	27	37
Staphylococcus aureus	21	28
CNS	8	11
HACEK organism	3	4
Other	8	11
Culture negative	7	9

TTE = transthoracic echocardiogram, TEE = transesophageal echocardiogram, CNS = coagulase-negative staphylococcus, HACEK = *Haemophilus aphrophilus*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, *Kingella kingae*.