

Infective Endocarditis in Children With Congenital Heart Disease Cumulative Incidence and Predictors

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Background—The American Heart Association guidelines for prevention of infective endocarditis (IE) in 2007 reduced the groups of congenital heart disease (CHD) patients for whom antibiotic prophylaxis was indicated. The evidence base in CHD patients is limited. We sought to determine the risk of IE in children with CHD.

Methods and Results—We performed a population-based analysis to determine the cumulative incidence and predictors of IE in children (0–18 years) with CHD by the use of the Quebec CHD Database from 1988 to 2010. In 47 518 children with CHD followed for 458 109 patient-years, 185 cases of IE were observed. Cumulative incidence of IE was estimated in the subset of 34 279 children with CHD followed since birth, in whom the risk of IE up to 18 years of age was 6.1/1000 children (95% confidence interval, 5.0–7.5). In a nested case-control analysis, the following CHD lesions were at highest risk of IE in comparison with atrial septal defects (adjusted rate ratio, 95% confidence interval): cyanotic CHD (6.44, 3.95–10.50), endocardial cushion defects (5.47, 2.89–10.36), and left-sided lesions (1.88, 1.01–3.49). Cardiac surgery within 6 months (5.34, 2.49–11.43) and an age of <3 years (3.53, 2.51–4.96; reference, ages 6–18) also conferred an elevated risk of IE.

Conclusions—In a large population-based cohort of children with CHD, we documented the cumulative incidence of IE and associated factors. These findings help identify groups of patients who are at the highest risk of developing IE. (*Circulation*. 2013;128:1412-1419.)

Key Words: congenital ■ endocarditis ■ epidemiology ■ heart defects, congenital

Congenital heart disease (CHD) represents a predisposing cardiac condition for the development of infective endocarditis (IE) and is increasing in prevalence.^{1,2} Improved survival of patients with CHD, in particular those with severe defects,³ has implications on the size of the population and the types of CHD lesions among patients at risk of IE. In addition, the use of prosthetic material to correct or palliate CHD lesions puts these patients at a higher risk of IE.

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In developed countries, CHD is the most prevalent underlying cardiac condition in children with IE.^{4–12} However, the risk of IE in a population-based cohort of children with CHD has never been reported, and the identification of CHD lesions at highest risk of IE has relied primarily on case series reports. Comparisons of risk of IE between cardiac conditions are 1 important consideration in the development of IE prevention guidelines. The American Heart Association guidelines for the prevention of IE were revised in 2007 with restrictions in

the groups of patients for whom antibiotic prophylaxis was indicated before invasive medical procedures.¹³ In 2008, the development group of the National Institute for Health and Clinical Excellence clinical guidelines made 2 research recommendations regarding prophylaxis against IE, one of which was: “What is the risk of developing IE in those with acquired valvular disease and structural congenital heart disease? Such research should use a population-based cohort study design to allow direct comparison between groups and allow estimation of both relative and absolute risk.”¹⁴

We sought to address these questions in patients with CHD by determining the cumulative incidence and predictors for the development of IE in a large population-based cohort of affected children.

Methods

Data Sources

Quebec is Canada’s second most populated province with nearly 8 million inhabitants.¹⁵ A unique healthcare number is assigned

Received February 5, 2013; accepted July 19, 2013.

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Circulation is available at <http://circ.ahajournals.org>

DOI: 10.1161/CIRCULATIONAHA.113.001827

to individuals at birth and systematically links all medical services rendered during the life course. All encounters with the healthcare system are recorded in the province's administrative databases—the hospital discharge summary and the medical service claims database—which collectively contain comprehensive longitudinal information on all hospital admissions and discharge diagnoses, inpatient and outpatient diagnostic and therapeutic procedures, and patients' demographic characteristics. Access to health care is universal, and physicians must submit billing information to the government to be remunerated. These factors promote the completeness of medical records for all residents of Quebec.

A population-based cohort of patients with CHD during the period 1983 to 2010 had been previously derived by identifying all patients with at least 1 CHD diagnosis, cross-referencing all CHD-related data in the source databases (including outpatient and inpatient CHD diagnoses, physicians' specialty, and CHD-specific surgical procedures) linked via an encrypted healthcare number, and using a hierarchical algorithm to assign 1 or 2 final CHD diagnoses to each patient.² The Quebec CHD Database thus ensured province-wide inclusion of patients with CHD and their long-term follow-up.

Conduct of this study was approved by McGill University Health Center ethics board.

Study Population

The study population consisted of all patients in the Quebec CHD Database who were children (0–18 years of age) between January 1, 1988 and March 31, 2010 (Figure 1). To determine the cumulative incidence of IE, we analyzed patients who were born during our observation period and followed since birth. To determine the predictors of IE, we identified all children with IE during the observation period and matched each on calendar time with 20 controls.

Measurements

For all analyses, incident IE was defined as the first hospitalization with a principal or secondary discharge diagnosis of IE that occurred during the observation period. The index date was the date of hospital admission. The following *International Classification of Diseases, Ninth Revision* and *Tenth Revision* codes were used to define IE: 421.0, 421.1, 421.9, 424.9, I33, I38, and I39. IE cases that occurred in the year 1988 were observed in the preceding 9 months to ensure that there were no previous IE diagnoses and thus to exclude prevalent cases. To validate our outcome definition, a random sample of 63 patients with IE was independently reviewed

by 2 CHD experts (A.J.M. and A.S.M.) by auditing and reconciliation of all information associated with a given patient's hospitalization for IE.

CHD lesions were grouped as follows: lesions most likely to be cyanotic at birth (tetralogy of Fallot, univentricular heart, complete transposition complex, truncus arteriosus, hypoplastic left heart syndrome); endocardial cushion defects; left-sided lesions (coarctation of the aorta, aortic stenosis/insufficiency, mitral stenosis/insufficiency); right-sided lesions (Ebstein anomaly, anomalies of the pulmonary artery or pulmonary valve, congenital tricuspid valve disease); atrial septal defect (ASD); ventricular septal defect (VSD); patent ductus arteriosus (PDA); and other CHD (other or unspecified congenital anomalies).²

Cardiac surgery included valve, shunt, or other cardiac surgical operations, congenital or noncongenital,¹⁶ performed before the index date.

Study Design

The cumulative incidence of IE was estimated in the cohort of children born during the observation period, with time zero set at birth and follow-up continued until 18 years of age, time of IE, death, or administrative censoring, whichever came first.

A nested, calendar time–matched case-control design with risk set sampling was used to analyze the predictors of IE. All cases of IE and a random sample of controls, matched on the calendar day when a case occurred, were nested in the total person-time as children. Risk sets were defined by the calendar day when a case of IE occurred. To minimize sparse data issues, we sampled a large number of controls per case, similarly to other studies.¹⁷ A random sample of 20 controls per case was drawn from each risk set.

Statistical Analysis

Overall and lesion group–specific cumulative incidence of IE was estimated as the complement of the Kaplan-Meier estimator. Cumulative incidence was also computed with adjustment for the competing risk of death by summing to time t the product of the Kaplan-Meier estimator of the overall survival function, $S(t - 1)$, with the hazard of death at t .¹⁸ This adjustment did not change the results, however. Overall and lesion group–specific incidence rate of IE were computed in the same population in which the cumulative incidence was described, defined as the number of first cases of IE divided by the total person-time at risk, with confidence intervals computed based on the Poisson distribution.

Characteristics of children with IE and their calendar day–matched controls were described with absolute numbers, proportions, and median/interquartile ranges. Predictors of IE were selected a priori based on clinical relevance. The following variables were assessed: cardiac surgery 6 months before the index date (yes/no); CHD lesions (as described in Measurements); age (0–3 years, 3–6 years, 6–18 years); and sex. Owing to matching at the design stage, the predictors of IE were analyzed by using conditional logistic regression; exact logistic regression was used if data were sparse.¹⁹ From these analyses we report rate ratios and their corresponding 95% confidence intervals.²⁰

In secondary analyses, cyanotic CHDs were grouped into conotruncal abnormalities (tetralogy of Fallot, transposition complex, truncus arteriosus) and single-ventricle states (univentricular heart, hypoplastic left heart syndrome) to further assess the risk of IE within this group. Cyanotic CHD and left-sided lesions were also separated into the constituent defects to test for heterogeneity of IE risk among lesions of the same CHD category. In addition, the impact of recent cardiac surgery during time windows of 3 and 12 months before the index date was examined. Finally, to discriminate between operated and unoperated patients in lesions found to be at elevated risk of IE, cyanotic CHD, endocardial cushion defects, and left-sided lesions were stratified based on a previous history of cardiac surgery from birth to 6 months before the time of matching. The latter analysis was restricted to children born during the observation period, among whom all surgical procedures undergone since birth could be ascertained.

Analyses were performed by using Stata version 11 (StataCorp, TX).

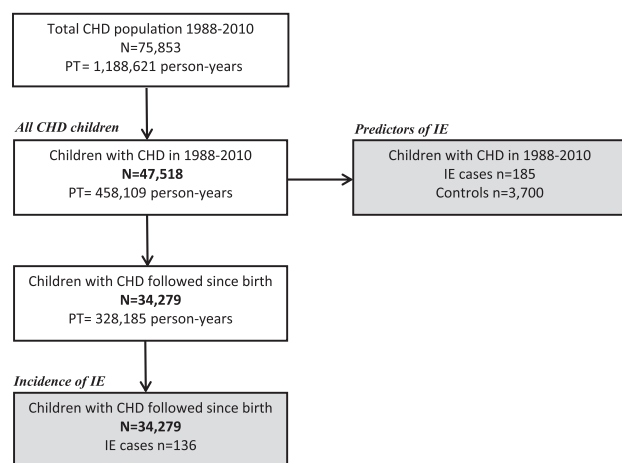


Figure 1. Derivation of the study population. CHD indicates congenital heart disease; IE, infective endocarditis; and PT, person-time.

Results

Cumulative Incidence of IE

Of 34 279 children who were followed since birth and contributed 328 185 person-years up to 18 years of age, 136 cases of IE were observed. The distribution of CHD lesions in the incidence cohort is shown in Table 1. The cumulative incidence of IE from birth to 18 years of age, in all CHD lesions combined, was 6.1 first cases per 1000 children (95% confidence interval [CI], 5.0–7.5) (Figure 2). This corresponded to an incidence rate of 4.1 per 10 000 person-years (95% CI, 3.5–4.9). The lesion group–specific cumulative incidences of IE by equal time intervals of 6 years and the incidence rates are presented in Table 2. The lesion group–specific cumulative incidences per 1000 children up to 18 years of age (95% CI) were as follows: cyanotic CHD, 31.0 (22.5–42.7); endocardial cushion defects, 11.1 (5.4–22.9); left-sided lesions, 7.9 (4.4–14.0); right-sided lesions, 4.2 (1.5–11.5); PDA, 3.2 (1.4–7.1); VSD, 3.2 (1.9–5.3); ASD, 3.0 (1.9–4.8); and other CHD, 5.5 (2.9–10.6). No IE events were observed in children with PDA past 4 years of age.

Predictors of IE

In 47 518 children followed for 458 109 person-years, we observed 185 cases of IE. Analysis of predictors of IE involved comparison of patients with IE and their 3700 calendar time–matched controls from the full population of children with CHD. Table 3 shows the baseline characteristics of the IE cases and controls. Cases and controls differed with respect to age, distribution of CHD lesions, and recent exposure to cardiac surgery. The most common CHD group among children with IE were cyanotic CHD lesions, present in 34% of cases. Although the next most frequent defects among cases were ASD (16%) and VSD (15%), their proportions were reduced in comparison with controls (27% each).

In multivariate analysis, children who had undergone cardiac surgery in the previous 6 months were > 5 times more likely to develop IE than those who had not (adjusted rate

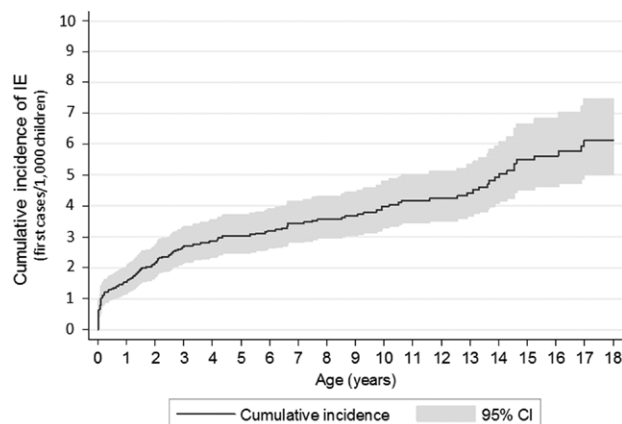


Figure 2. Cumulative incidence of IE from birth to 18 years of age in children with CHD. CHD indicates congenital heart disease; CI, confidence interval; and IE, infective endocarditis.

ratio [RR], 5.34; 95% CI, 2.49–11.43). Risk of IE varied substantially across the CHD lesions (Wald test $P < 0.001$, $\chi^2 = 94.2$, $df = 7$). Relative to ASD, the following lesions were most strongly associated with an elevated risk of IE: cyanotic CHD (adjusted RR, 6.44; 95% CI, 3.95–10.50), endocardial cushion defects (adjusted RR, 5.47; 95% CI, 2.89–10.36), and left-sided lesions (adjusted RR, 1.88; 95% CI, 1.01–3.49). Young age was a strong predictor of IE: in comparison with those aged 6 to 18, children < 3 years of age were at higher risk of IE (adjusted RR, 3.53; 95% CI, 2.51–4.96), but not those 3 to 6 years of age (adjusted RR, 0.91; 95% CI, 0.54–1.51). Owing to the rarity of IE events, the interaction of age and CHD lesions could not be formally assessed. No important association was observed between male sex and IE (adjusted RR, 1.09; 95% CI, 0.80–1.50) (Figure 3A).

Further breakdown of cyanotic CHD group into conotruncal abnormalities and single-ventricle states showed that the relative risks of IE (with the use of ASD as reference) were similar (adjusted RR, 6.36; 95% CI, 3.81–10.59; and adjusted RR, 5.94; 95% CI, 2.73–12.93; respectively; Wald test probability value for heterogeneity = 0.86, $\chi^2 = 0.03$, $df = 1$). When individual CHD defects were assessed separately, there were too few IE cases per lesion to derive useful conclusions. The effect estimates were comparable, however, and there was no evidence of heterogeneity of IE risk among defects of either the cyanotic CHD category (Wald test $P = 0.40$, $\chi^2 = 4.1$, $df = 4$) or left-sided lesions category (Wald test $P = 0.75$, $\chi^2 = 0.57$, $df = 2$), justifying the grouping of these defects together. Risk of IE associated with recent cardiac surgery was examined at time intervals 3, 6, and 12 months after surgery. At each interval, a markedly larger proportion of IE patients underwent surgery in comparison with controls. The relative risk of IE was particularly high in the immediate postoperative period, and, although it continued to be elevated at 12 months after surgery, this was primarily attributable to the concentration of IE episodes in the first 0 to 6 months of that period (Figure 3B).

In children followed since birth, cyanotic CHDs were stratified based on a previous history of cardiac surgery. Relative to ASD, both unoperated and operated cyanotic

Table 1. Distribution of CHD Lesions in Children Followed Since Birth, 1988 to 2010

CHD Lesions	No. of Children (%)	Person-Years of Follow-Up
Cyanotic CHD	2196 (6)	21 757
Endocardial cushion defects	975 (3)	10 389
Left-sided lesions	2811 (8)	31 974
Right-sided lesions	2201 (6)	20 574
Patent ductus arteriosus	2170 (6)	17 329
Ventricular septal defect	8646 (25)	84 386
Atrial septal defect	12 343 (36)	111 989
Other CHD	2937 (9)	29 787
Total	34 279 (100)	328 185

Numbers may not add up because of rounding. The absolute numbers in this table do not reflect the birth prevalence of CHD lesions. Some defects may be asymptomatic early in life and only captured after an extended observation period. CHD indicates congenital heart disease.

Table 2. Lesion Group–Specific Cumulative Incidence and Incidence Rate of IE in Children With CHD

CHD Lesions	Cumulative Incidence (95% CI) per 1000 Children			Incidence Rate (95% CI) per 10000 Person-Years
	0–6 y	0–12 y	0–18 y	
Cyanotic CHD	16.8 (11.9–23.8)	23.3 (17.0–31.8)	31.0 (22.5–42.7)	20.7 (15.4–27.7)
Endocardial cushion defects	5.5 (2.3–13.1)	8.7 (4.1–18.6)	11.1 (5.4–22.9)	7.7 (3.9–15.4)
Left-sided lesions	2.7 (1.3–5.7)	4.8 (2.6–8.7)	7.9 (4.4–14.0)	4.4 (2.6–7.4)
Right-sided lesions	2.3 (1.0–5.5)	2.3 (1.0–5.5)	4.2 (1.5–11.5)	2.9 (1.3–6.5)
Patent ductus arteriosus	3.2 (1.4–7.1)	3.2 (1.4–7.1)	3.2 (1.4–7.1)	3.5 (1.6–7.7)
Ventricular septal defect	2.0 (1.2–3.2)	2.4 (1.5–3.8)	3.2 (1.9–5.3)	2.4 (1.5–3.7)
Atrial septal defect	1.9 (1.3–2.9)	2.2 (1.5–3.4)	3.0 (1.9–4.8)	2.3 (1.6–3.4)
Other CHD	2.9 (1.4–5.8)	3.7 (1.8–7.3)	5.5 (2.9–10.6)	3.7 (2.0–6.7)
Overall	3.2 (2.6–3.9)	4.2 (3.5–5.1)	6.1 (5.0–7.5)	4.1 (3.5–4.9)

CHD indicates congenital heart disease; CI, confidence interval; and IE, infective endocarditis.

CHD patients were at high risk of IE (adjusted RR, 7.56; 95% CI: 4.03–14.18 and adjusted RR, 9.22; 95% CI, 4.39–19.34, respectively). Previously unoperated endocardial cushion defects and left-sided lesions were also at elevated risk of IE (adjusted RR, 3.00; 95% CI, 1.06–8.51 and adjusted RR, 2.35; 95% CI, 1.16–4.7, respectively) (Table 4), whereas the rate ratios in operated patients could not be reliably estimated in these lesions because of sparse data.

Discussion

We report the childhood risk of IE in a large, population-based cohort of patients with CHD as 6.1/1000 from birth to

18 years of age, corresponding to 4.1 cases/10000 person-years. Cyanotic CHD lesions, left-sided lesions, and endocardial cushion defects were associated with increased risk of IE acquisition in childhood. The relative risk of developing IE was substantially elevated during the 6-month postoperative period of cardiac surgery and in children <3 years of age.

Cumulative Incidence of IE

To our knowledge, this is the first study to estimate the cumulative incidence of IE in children with CHD. In adults with CHD, the overall incidence rate of IE has been reported as 11 per 10000 person-years in the CONCOR database in the

Table 3. Characteristics of Children (0–18 Years of Age) With IE and Their Calendar Time–Matched Controls

Characteristic	IE cases (n=185), n (%)	Controls (n=3700), n (%)	Unadjusted Rate Ratio (95% CI)
Cardiac surgery 6 mo before*	17 (9)	25 (1)	15.52 (8.08–29.80)
Valve surgery 6 mo before	3 (2)	8 (0)	7.50 (1.28–31.25)†‡
Shunt surgery 6 mo before	13 (7)	13 (0)	21.06 (9.59–46.25)†
Other cardiac surgery 6 mo before	13 (7)	25 (1)	11.67 (5.76–23.63)†
CHD type			
Cyanotic CHD	62 (34)	348 (9)	6.38 (4.02–10.13)
Endocardial cushion defects	18 (10)	154 (4)	4.37 (2.35–8.15)
Left-sided lesions	18 (10)	414 (11)	1.57 (0.86–2.88)
Right-sided lesions	7 (4)	216 (6)	1.12 (0.49–2.59)
Patent ductus arteriosus	6 (3)	161 (4)	1.33 (0.54–3.27)
Ventricular septal defect	27 (15)	988 (27)	0.95 (0.56–1.62)
Atrial septal defect	29 (16)	1004 (27)	Reference
Other CHD	18 (10)	415 (11)	1.54 (0.84–2.81)
Age, y			
Median (IQR)	3.5 (0.6–10.2)	7.6 (3.6–12.2)	
0–3	89 (48)	788 (21)	3.30 (2.40–4.53)
3–6	20 (11)	698 (19)	0.84 (0.51–1.39)
6–18	76 (41)	2214 (60)	Reference
Male sex	97 (52)	1761 (48)	1.22 (0.90–1.64)

Cardiac surgery subcategories do not add up to the total because the procedures performed in 1 operation may fall under >1 category. Percentages do not add to 100% because of rounding. CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; and IQR, interquartile range.

*6 mo before is with respect to the index date for cases and the time of matching for controls.

†These are combined into a single variable in the multivariate model.

‡Estimated with exact logistic regression owing to sparse data.

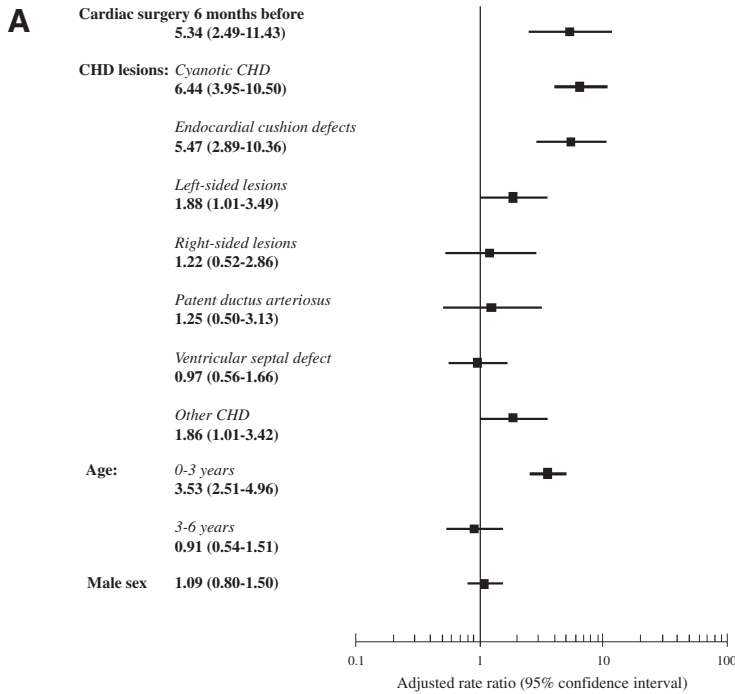
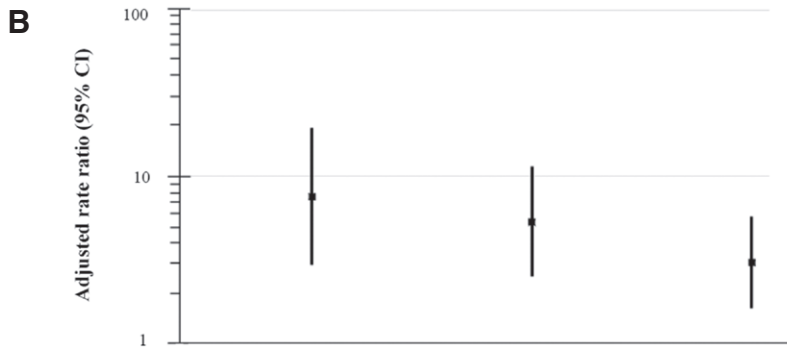


Figure 3. A, Predictors of IE in children with CHD. CHD lesions indicate reference category is atrial septal defect. Age indicates reference category is age group 6-18 years. “6 months before” is with respect to index date for the cases and time of matching for the controls. **B**, Association of recent cardiac surgery and IE. Rate ratios were obtained from separate conditional logistic regression models with different time windows for cardiac surgery and adjusted for CHD lesion, age and sex. Reference category: no cardiac surgery within the same time window. CHD indicates congenital heart disease; CI, confidence interval; and IE, infective endocarditis.



Time	0-3 months	0-6 months	0-12 months
IE cases (of 185)	12	17	20
Controls (of 3,700)	13	25	49

Netherlands.²¹ The overall rate of IE in our study was ≈3 times lower than the published estimate in adults with CHD. The reduced frequency of IE in children versus adults with CHD parallels the trend in the general population, where the incidence of IE in adults ranges from 15 to 60 cases per million person-years,²² whereas in children it is lower at 3.9 to 6.4 cases per million person-years.^{10,23}

Risk Factors for IE

The risk of IE varied markedly across the CHD lesions. Collectively, lesions associated with cyanosis at birth had the highest incidence of IE. The observed IE rate was higher than that previously reported after definitive repair of 2 of the defects in this category (dextrotransposition of great arteries and tetralogy of Fallot),²⁴ an expected result given that our study population was not restricted to children with corrected CHD and that surgical repair reduces the risk of IE for at least some of these defects.^{4,6}

Children with endocardial cushion defects or left-sided lesions were also at increased IE risk. The relatively high IE

risk observed in children with left-sided lesions was in line with several studies that have underscored the risk of IE in patients with left ventricular outflow obstruction lesions,^{9,13,17,20,21,26,27} although, in absolute terms, the IE rate in our population of children with left-sided lesions was lower than previously documented.²⁵ The severity of the defect is important for the risk of IE,²⁵ and the population of adults in whom the reported rates had been estimated may represent more severe conditions.

As expected, IE was less common in right-sided than in left-sided lesions. In children with PDA, IE risk was limited to patients <4 years of age, consistent with reports that have documented PDA as a frequent underlying condition in infants and neonates with IE,²⁶ but not in patients with ligated PDA,^{21,27} suggesting that the correction of the defect may explain the age-related reduction in IE risk. In children with VSD, the IE incidence represented a lower frequency of IE in this study than in the previously reported rates in adults with VSD,^{21,25} which may be attributable to a greater proportion of complex VSDs among adults and more isolated VSDs in children. Finally, isolated secundum ASD is considered a

Table 4. CHD Lesions at Elevated Risk of IE Stratified by History of Cardiac Surgery

CHD Lesions	IE Cases, n (%)	Controls, n (%)	Adjusted Rate Ratio (95% CI)
Cyanotic CHD	45	178	
Unoperated	27 (60)	100 (56)	7.56 (4.03–14.18)
Operated	18 (40)	78 (44)	9.22 (4.39–19.34)
Endocardial cushion defects	8	84	
Unoperated	5 (63)	51 (61)	3.00 (1.06–8.51)
Operated	3 (37)	33 (39)	—*
Left-sided lesions	14	253	
Unoperated	13 (93)	233 (92)	2.35 (1.16–4.73)
Operated	1 (7)	20 (8)	—*

Analysis was performed in the subset of children followed since birth. History of cardiac surgery was measured from birth to 6 months before time of matching and did not include catheterization procedures. Adjustment was for age, sex, and cardiac surgery in the previous 6 months. CHD categories not stratified by history of cardiac surgery (right-sided lesions, VSD, PDA, and other CHD) are not shown. The reference CHD category is atrial septal defects (26 IE cases, 928 controls). CHD indicates congenital heart disease; CI, confidence interval; IE, infective endocarditis; PDA, patent ductus arteriosus; and VSD, ventricular septal defect.

*Covariate adjustment is impossible because of sparse data.

lesion with a negligible IE risk. However, in this study, as in the CONCOR database of adults with CHD,²¹ the IE risk in ASD was higher than in the general population. This may be attributable to the joint presence of conditions that increase the IE risk, such as mitral valve prolapse or regurgitation, or the inclusion of some patients with primum ASD that may have been misclassified and not included in the endocardial cushion defects group, leading to overestimation of IE risk in children with ASD.

Cardiac surgery within 6 months conferred a 5-fold increase in IE risk. The elevated IE risk is consistent with previous studies^{7,11,24} and with the observation that endothelialization of prosthetic material, often introduced by cardiac surgery, occurs within 6 months following the procedure.¹³ Microorganisms introduced through medical procedures or routine daily activities may be more likely to attach to the site of repair during this time. It is also possible that cardiac surgery itself may have been a bacteremia-producing procedure that led to IE.

Elevated IE risk in early childhood has been reported in studies of children with CHD,^{11,28} and in children from the general population, as well,¹² and is probably multifactorial. Many patients undergo surgery for their CHD lesions early in life, which may reduce the IE risk, resulting in lower relative risk at older ages. Indeed, our data show that IE risk is highest in children 0 to 3 years of age. In this age group, surgical procedure rates may not have yet reached those seen in general pediatric cardiology practice. Also, the use of intravascular catheters and iatrogenic devices at young age may put these children at risk of IE.²⁹

Similarly to a study on a US national sample of pediatric IE hospitalizations,¹² but in contrast to other IE reports in adults,^{21,30} we observed comparable IE frequency in boys and girls. Possibly, high-risk behaviors¹ and other lifestyle

factors may be less likely to differ between boys and girls during childhood.

Strengths and Limitations

The population-based observations, availability of longitudinal data on patients, and the large size of the CHD cohort constitute major strengths of this work and a point of departure from other studies of IE, which relied on CHD patients from single institutions and referral centers to find lesions at high risk of IE,^{27,31,32} on case series of patients with IE to determine frequency of CHD types,^{17–30} or which analyzed hospital admissions for IE without longitudinal individual patients' data.^{12,33,34} Although our data sources ensured the province-wide inclusion of children with CHD into the cohort, they are prone to misclassification error and lack clinical information, which can limit the validity and generalizability of the data.

To minimize misclassification of CHD, the diagnosis was determined by a comprehensive evaluation of all CHD-related data, including all CHD codes, surgical codes, and manual review of samples of the data.² Misclassification of this multicategorical exposure could have biased the effect estimates of CHD lesions in either direction. It should be noted that the data in Table 1 do not represent the birth prevalence of CHD. Specifically, the excess in absolute numbers of ASDs relative to VSDs reflects the ability to capture more ASDs with a long duration of follow-up that may have been asymptomatic early in life. This is in contrast to VSDs, which usually present with murmur and are identified early. Indeed, the birth prevalence of VSD from our database² is the same as that published previously.³⁵

We measured IE as a hospitalization in administrative records, similarly to several large-scale studies designed to obtain absolute measures of IE frequency,^{12,33,34} and consistently with the high risk of complications in children with IE and the expectation that antibiotic treatment would have been initiated in the hospital.^{36,37} In addition, to ensure the best possible accuracy of the IE diagnosis, samples of patients were audited independently by 2 CHD experts. Misclassification of IE could result in underestimation or overestimation of the cumulative incidence of IE, and in the analysis of predictors, it would lead to bias toward the null value if independent of and nondifferential with respect to the predictors. Finally, the clinical definition of IE was not available, and, during the study period, the clinical criteria to establish the IE diagnosis have been modified,^{38,39} use of echocardiography has increased,⁴⁰ and microbiological techniques have advanced.⁴¹ Although these factors could not be directly quantified, our design where we matched IE cases and controls on calendar day is expected to reduce any bias away from the null value owing to the ascertainment of IE.

The risk factors examined were limited by the nature of the data. Oral health and dental hygiene, which may be important measures of random bacteremias from daily activities, were not measured. Data on prophylactic antibiotic use before medical procedures were also not available. This lack of data prevented the assessment of the effectiveness of prophylactic antibiotic use in averting IE and the adjustment for potential confounding, if differentially administered across patient subpopulations. Moreover, dental procedures could not be

systematically ascertained for all children, and their impact was therefore not assessed. However, our study was not designed to examine the impact of IE prophylaxis. The effect of cardiac surgery is complex and depends on the type of surgery and the underlying CHD. We chose to focus our analysis on cardiac surgery in the previous 6 months. The impact of cardiac surgery from birth to 6 months before the index date was investigated in cyanotic CHD, left-sided lesions, and endocardial cushion defects. However, because of the rarity of IE events, such analysis could not be performed for all CHD types. The infrequency of IE also prevented the formal assessment of interactions between variables and the investigation of CHD lesions individually. Although CHD lesions were grouped into categories of comparable IE risk, not all constituent lesions of the group shared identical IE susceptibility, leading to within-category residual confounding from CHD type. Last, the impact of spontaneous VSD closures could not be assessed; and, within the cyanotic CHD group, the data did not permit a distinction between cyanosis in infancy (associated with the native anatomy) versus chronic cyanosis.

IE prevention guidelines on antibiotic prophylaxis require consideration of several questions, including protective efficacy and the cost-effectiveness of prophylaxis, the relative importance of everyday bacteremias versus invasive procedures in causing IE, and the direct comparison of absolute and relative risk of IE between cardiac conditions. This study addressed the latter question in the context of children with CHD. In line with the 2007 American Heart Association guidelines, cyanotic CHD lesions and cardiac surgery in the previous 6 months were strongly associated with IE in this study. However, we found that patients with left-sided lesions or endocardial cushion defects were also at elevated IE risk. Currently, these lesions are not indicated for prophylaxis unless they meet other eligibility criteria, such as previous IE episodes or cardiac prostheses. Our findings help identify groups of children with CHD who are at highest risk of IE, inform cost-effectiveness analyses of antibiotic use by providing data on numbers of population at risk and IE cases, and contribute to better interpretation of data collected since the change in guidelines.

Sources of Funding

Dr Kaufman is funded by the Canada Research Chairs program. Drs Marelli, Ionescu-Ittu, and Pilote are funded by the Fonds de la recherche en santé du Québec. Drs Marelli and Mackie are funded by the Heart and Stroke Foundation of Canada and the Canadian Institutes of Health Research. Dr Pilote holds a James McGill Chair at McGill University.

Disclosures

None.

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CLINICAL PERSPECTIVE

This is the first population-based study to estimate the cumulative incidence of infective endocarditis (IE) in children with congenital heart disease (CHD). In a large cohort of children with CHD in Quebec followed during 1988 to 2010, we determined the absolute and relative risk of IE in CHD lesion groups. Overall, the cumulative incidence of IE from birth to 18 years of age was 6.1 first cases/1000 children (corresponding to 4.1 first cases/10000 person-years). The risk of IE varied markedly across the CHD lesion groups, with the greatest risk observed in children with cyanotic CHD, endocardial cushion defects, or left-sided lesions. Recent cardiac surgery and young age also conferred an elevated IE risk. These results help identify groups of children with CHD who are at the highest risk of IE acquisition, and they fill 1 important gap in the evidence base for IE prevention recommendations. In a comparison of these findings with the patient groups indicated for prophylaxis in the 2007 American Heart Association guidelines, in line with the current recommendations, cyanotic CHD and cardiac surgery in the previous 6 months were strongly associated with IE. However, we showed that 2 other patient groups, children with endocardial cushion defects or left-sided lesions, were also at elevated risk of IE. Patients with these defects were at increased IE risk even if they had no previous cardiac surgery or history of IE. Our findings may contribute to informing IE prevention guidelines.