Contemporary epidemiology of infective endocarditis in patients with congenital heart disease: A UK prospective study☆

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Objectives Infective endocarditis is a life-threatening complication of congenital heart disease (CHD), but there are few studies concerning the contemporary risk profile, preceding invasive procedures and outcomes in this patient population. The aim of this study was to investigate the epidemiology of infective endocarditis (IE) in patients with CHD.

Methods Cases of IE in children and adults with CHD were prospectively recorded as part of the UK National Institute for Cardiovascular Outcomes Research (NICOR) National Congenital Heart Disease Audit. Patients were entered into the database between April 2008 and March 2016.

Results Eight hundred episodes of IE were recorded in 736 patients with CHD. Sixty-five patients (9%) were infants (aged <1 year), 235 (32%) were children (aged 1–15 years), and 436 (59%) were adults (aged >15 years). The most common diagnoses were Tetralogy of Fallot (n = 150, 22.8%), ventricular septal defect (n = 129, 19.6%) and bicuspid aortic valve (n = 70, 10.7%). Dental procedures preceded 67 of 635 episodes (11%) of IE, and non-dental invasive procedures preceded 177 of 644 episodes (27.4%). The most common causative organisms were streptococci, accounting for 40% of cases. Overall in-hospital mortality was 6.7%. On multivariable analysis, adverse factors associated with in-hospital mortality were staphylococcal infection and presence of an underlying atrioventricular septal defect.

Conclusions Infective endocarditis in patients with CHD is an ongoing clinical challenge. In contemporary practice in tertiary congenital centers, 1 of 15 patients do not survive to hospital discharge. Streptococci remain the most common causative organism, and antecedent dental or medical procedures were undertaken in a significant minority in the 3 months before diagnosis. The presence of an atrioventricular septal defect or staphylococcal infection is associated with significantly increased risk of early mortality. (Am Heart J 2019;215:70-7.)

Infective endocarditis (IE) is a leading cause of morbidity and mortality in patients with congenital heart disease (CHD).[1,2] The risk of the condition in adults with CHD is 20 to 50 times that of the general population, with a 10-year cumulative incidence of approximately 1%.[3-5] CHD is linked to the development of IE through endothelial shear stress, the presence of intracardiac prosthetic material (valves and conduits) and implanted cardiac electronic devices, and recurrent healthcare procedures. Over the last 30 years there have been significant advances in CHD care, and the number of patients with repaired or palliated defects has expanded significantly.[6,7] In parallel, the microbiological characteristics of IE have changed, with an increasing incidence of staphylococcal disease and healthcare-associated infection.[8]

In this context of evolving patient demographic and disease, characterization of the burden and epidemiology of IE in patients with CHD is important to define preventive strategies and improve patient outcomes. The importance of invasive dental and medical procedures as a trigger for IE in patients with CHD remains unclear.[9] In 2008 the UK National Institute for Health and

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Table 1. Patient demographics

	n	%
Total number of episodes, n	800	
Total number of patients, n	736	
Female, n (%)	272	37%
Age, median (min, LQ, UQ, max)	20	(0,8,35,77)
<1 year	65	9%
1–15 years	235	32%
>15 years	436	59%

Care Excellence (NICE) advised against oral antibiotic prophylaxis for prevention of IE in all patient groups due to a lack of evidence for efficacy. Whether this recommendation has been followed by cardiologists caring for patients with CHD is unknown.[10] Furthermore, given the relative rarity and heterogeneity of CHD, the factors influencing patient outcome are poorly described.

The aims of this study were: first, to analyze the contemporary epidemiology of IE in pediatric and adult patients with CHD; second, to identify the frequency of specific potential triggering procedures prior to diagnosis, and the current use of antibiotic prophylaxis; and third, to analyze factors affecting short term outcomes in this high-risk population.

Table 2. Primary CHD lesion in patients with infective endocarditis

Diagnosis	n	%	Adult	Child	Infant
Tetralogy of Fallot*	150	22.8%	84	56	10
VSD	129	19.6%	76	46	7
Bicuspid aortic valve	70	10.7%	59	11	0
Aortic valve disease (AS / AR)	57	8.7%	46	11	0
Discordant VA connections (TGA)	42	6.4%	20	16	6
Coarctation of the aorta	33	5.2%	26	6	1
Mitral valve anomaly	31	4.7%	22	8	1
Common arterial trunk	31	4.7%	7	21	3
AVSD	25	3.8%	6	11	8
ASD**	18	2.7%	8	5	5
Hypoplastic left heart syndrome	14	2.1%	0	3	11
Pulmonary valve anomaly	14	2.1%	13	0	1
Congenitally corrected TGA	9	1.4%	7	2	0
Tricuspid valve anomaly	7	1.1%	6	1	0
PDA	7	1.1%	7	1	0
Functionally UVH***	6	0.9%	5	1	0
Other ****	14	2.1%	7	5	2
Unknown	79	10.7%	36	31	10

* Incl pulmonary atresia and TOF-type double-outlet right ventricle.
** Primum or subtype unspecified in 15/18.
*** Incl double inlet left ventricle, double inlet right ventricle, double outlet left ventricle mitral/tricuspid atresia.
**** Incl anomalous origin of coronary artery from pulmonary artery, discontinuous pulmonary arteries, pulmonary arterial stenosis, total anomalous pulmonary venous return, LV abnormality (unspecified), LV outflow tract obstruction, pulmonary vein stenosis, subaortic stenosis.

Methods

Ethical approval for NICOR audit data collection was provided by the U.K. National Institute and Governance Board Ethics and Confidentiality Committee. Cases of IE in children and adults with CHD who were managed at tertiary congenital centers were prospectively recorded as part of the UK NICOR National CHD Audit (NCHDA). The NCHDA included the United Kingdom and from 2010, the Republic of Ireland for pediatric patients (< 16 years). Patients were entered into the database between April 2008 and March 2016 by their supervising clinical team or database manager. Data collected included: age, gender, diagnosis of CHD, invasive medical or surgical procedure in a 3-month period prior to diagnosis (and use of antibiotic prophylaxis), causative organism (based on blood cultures) and outcome to hospital discharge. The diagnosis of infective endocarditis and all data collected was independently validated by the NCHDA Audit Officer at annual site visits to all tertiary Adult/Pediatric cardiac centers. No extramural funding was used to support this work.

Summary data are expressed as median with interquartile range, or absolute number with percentage, as appropriate. Where data were unavailable or unclear, the data point was excluded. Kaplan–Meier (KM) curves were drawn to show survival over time, incorporating a 95% confidence interval for KM point estimate. Cox proportional hazards modeling was used to identify baseline factors associated with adverse outcome. Variables considered in univariate and multivariable

Table 3. Incidence of invasive procedures and use of antibiotic prophylaxis in three months prior to an episode of infective endocarditis.

Invasive procedure, n (%)		Antibiotic prophylaxis n (%)
Dental procedure	**67 (11%)**	22 / 57 (39%)
Extraction(s)	36 (5.7%)	13 / 33 (39%)
Scaling	12 (1.9%)	4 / 11 (36%)
Other	19 (3.0%)	5 / 13 (38%)
None	568	
Unknown	165	
Other procedure	**177 (27%)**	
Cardiac catheterization	27 (4.1%)	
Venous line placement	25 (3.8%)	
GI or GU surgery	16 (2.5%)	8 /16 (50%)
Body piercing	6 (0.9%)	
Tattoo	2 (0.3%)	
Oronasopharyngeal procedure	2 (0.3%)	1 / 2 (50%)
Other	99 (15%)	83 / 99 (84%)
None	467	
Unknown	156	

Abbreviations: GI gastrointestinal; GU genitourinary.

Table 4. Microbiology of infective endocarditis

Culture result	n	%
Streptococci	280	40%
Staphylococci	230	33%
Enterococci	30	4%
Fungal	6	1%
Other	89	13%
Culture negative	71	10%
Total	706	

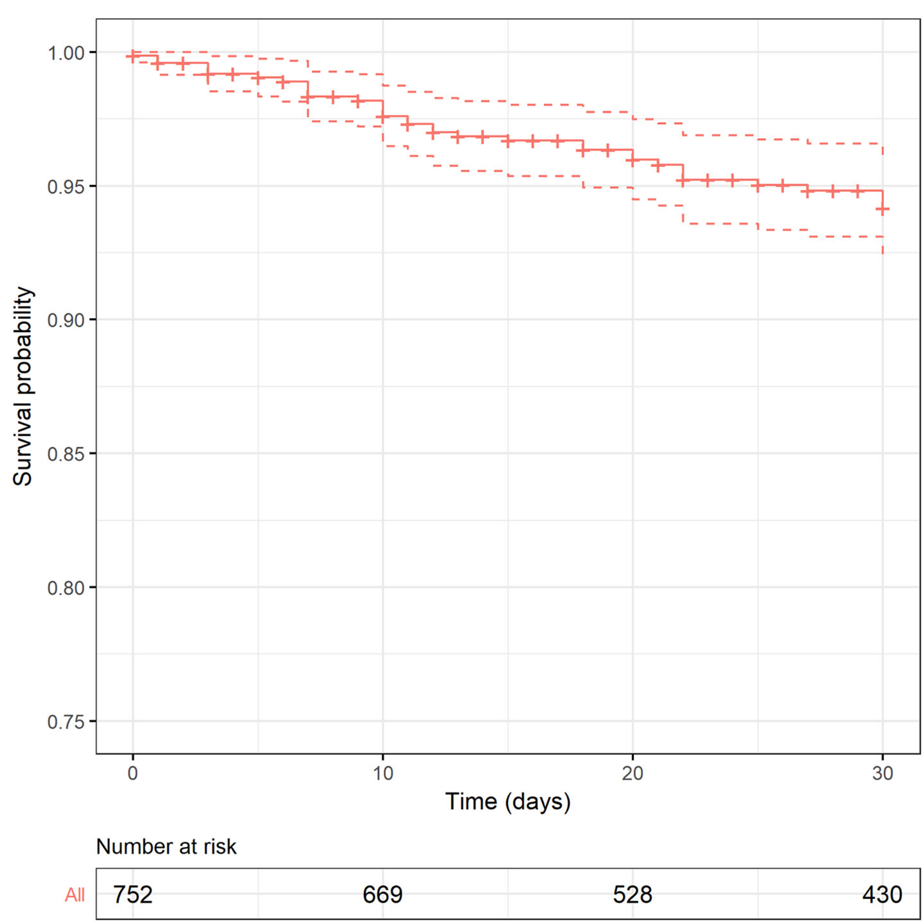
analyses were patient age group, gender, causative organism and CHD diagnosis. Graphical methods were used to check the proportional hazards assumption. Log (−log(S(t))) was plotted against time and checked for parallelism. There was no evidence of violation of the proportional hazards assumption. Age groups were defined as infant (<1 year), child (1-15 years) and adult (>15 years). Data were analyzed with Stata (StataCorp. 2017. Stata Statistical Software: Release 15. College Station, Tx: StataCorp LLC) and R (R: a language and environment for statistical computing. R Foundation for Statistical Computing, Vienna, Austria, http://www.R-project.org). A p value of <0.05 was defined as significant.

Results

Between April 2008 and March 2016, 800 episodes of IE were recorded in 736 patients with CHD across 27 centers in the United Kingdom and Ireland (Table 1).

The underlying primary congenital lesion was available for 659/736 patients (89.5%) (Table 2). The most common diagnosis was Tetralogy of Fallot (n = 150, 22.8%), followed by ventricular septal defect (n = 129, 19.6%) and bicuspid aortic valve (n = 70, 10.6%). In adults and children (>1 year), Tetralogy of Fallot was the

Figure 1



Kaplan–Meier analysis showing overall survival of congenital heart disease patients with infective endocarditis. The dashed lines show the 95% confidence interval for the point estimate.

most frequent primary diagnosis, accounting for 21.0% and 27.5% of cases, respectively. In infants, hypoplastic left heart syndrome was the most frequent underlying diagnosis, accounting for 20% of cases.

Data were available for preceding dental and non-dental procedures for 635/800 (79.4%) and 644/800 (80.5%) episodes, respectively. Dental procedures preceded 67/635 episodes (11%) of IE, with dental extraction preceding 36/635 episodes (5.7%) (Table 3). Non-dental invasive procedures were performed prior to 177/644 episodes (27.4%). The most common preceding invasive medical procedures were cardiac catheterization, venous line placement and gastrointestinal/genitourinary (GI/GU) surgery (Table 3). Data concerning the use of antibiotic prophylaxis were available for a subset of these invasive procedures. Despite UK guidance from the National Institute for Health and Clinical Excellence (NICE), antibiotic prophylaxis was used prior to dental procedures in 22/57 (39%), and prior to GI/GU surgery in 8/16 (50%) of cases.

Table 5. Risk factors for inpatient mortality on univariate and multivariable analysis (Cox-regression analysis)

Factor	Univariate analysis		Multivariable analysis	
	HR (95% CI)	P	HR (95% CI)	P
Patient factors				
Infant	3.1 (1.6–6.1)	.001**	2.0 (0.85–4.7)	.11
Male sex	0.51 (0.29–0.91)	.023*	0.58 (0.30–1.1)	.10
CHD diagnosis				
Tetralogy of Fallot	0.58 (0.26–1.3)	.19		
VSD	0.96 (0.45–2.1)	.92		
Bicuspid aortic valve	0.19 (0.026–1.4)	.1		
TGA	1.1 (0.33–3.4)	.91		
Coarctation of the aorta	0.45 (0.061–3.2)	.42		
Mitral valve anomaly	0.85 (0.21–3.5)	.82		
Common arterial trunk	1.9 (0.58–6)	.3		
AVSD	3.2 (1.4–7.7)	.0083**	3.0 (1.2–7.6)	0.017*
ASD	0.98 (0.13–7.1)	.98		
HLHS	3.9 (1.2–13)	.024*	3.2 (0.81–12.6)	0.096
Pulmonary valve anomaly	1.3 (0.17–9.2)	.81		
Congenitally corrected TGA	2 (0.28–15)	.48		
Tricuspid valve anomaly	2.3 (0.32–17)	.4		
Functionally UVH	0.56 (0.24–13)	.58		
PDA	3.6 (0.5–27)	.2		
Endocarditis factors				
Staphylococcal culture	2.3 (1.2–4.2)	.01*	2.0 (1.0–3.9)	.036*

Abbreviations: ASD atrial septal defect; AVSD atrioventricular septal defect; CHD congenital heart disease; CI confidence interval; HLHS hypoplastic left heart syndrome; HR hazard ratio; PDA patent ductus arteriosus; TGA transposition of the great arteries; VSD ventricular septal defect; UVH univentricular heart. *$P < .05$, **$P < .01$.

The microbial etiology of IE was available for 706/800 episodes (88%) (see Table 4). The most common causative organisms were streptococci, accounting for 40% of cases, while staphylococci were isolated in 33% of cases. Other organisms accounted for 13%, and fungi were isolated in 1%. Blood cultures were negative in 10%.

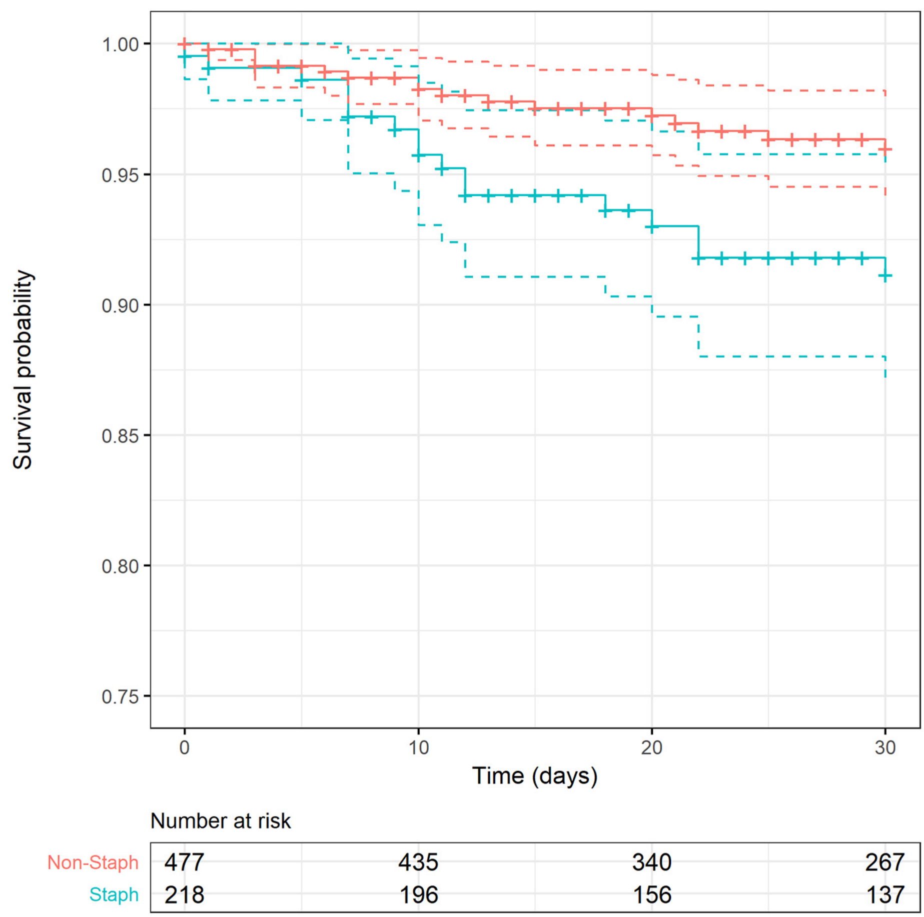
Outcome data were available for 705/800 episodes of IE (88%). Mortality at 30 days was 5.0% (Figure 1). Overall in-hospital mortality was 6.7%. The median length of stay was 36 days (interquartile range 20–52, range 1–433 days). We analyzed factors predictive of in-patient mortality (Table 5). On univariate analysis, infant age, male gender, staphylococcal infection, and a diagnosis of atrioventricular septal defect or hypoplastic left heart syndrome were associated with a significantly increased risk of in-hospital death. On multivariable analysis, staphylococcal infection (hazard ratio 2.0, 95% CI 1.0–3.9, $P = .036$; Figure 2) and a primary diagnosis of atrioventricular septal defect (HR 3.0, 95% CI 1.2–7.6, $P = .017$; Figure 3) remained significant risk factors for in-hospital mortality.

Next, we utilized this dataset to estimate the overall yearly incidence of IE in patients with CHD. Published estimates for the contemporaneous prevalence of CHD in England were available from a recent study which identified all patients with any form of CHD who were admitted to hospital between 2000 and 2008, using *ICD-10* and OPCS-4 codes.[3] The estimated total prevalence of CHD was 29,194 patients in England in 2008. The population in England accounts for 83.8% of the UK (UK Office for National Statistics). Assuming a proportional distribution of IE cases across the regions of the UK, we estimate a total of 670.4 episodes within the CHD population in England (n = 29,194) over an 8 year time period, equating to 83.8 episodes per 29,194 CHD population per year, or 1 episode per 348 per year.

Discussion

There are several key findings from this study. First, that there is substantial mortality due to IE in infants, children and adults across the spectrum of CHD. Second, a notable proportion of cases are preceded by an invasive medical or dental procedure, for which use of antibiotic prophylaxis is highly variable. Although UK guidelines advise against routine use of antibiotic prophylaxis, many congenital specialists in UK continue to follow guidelines

Figure 2



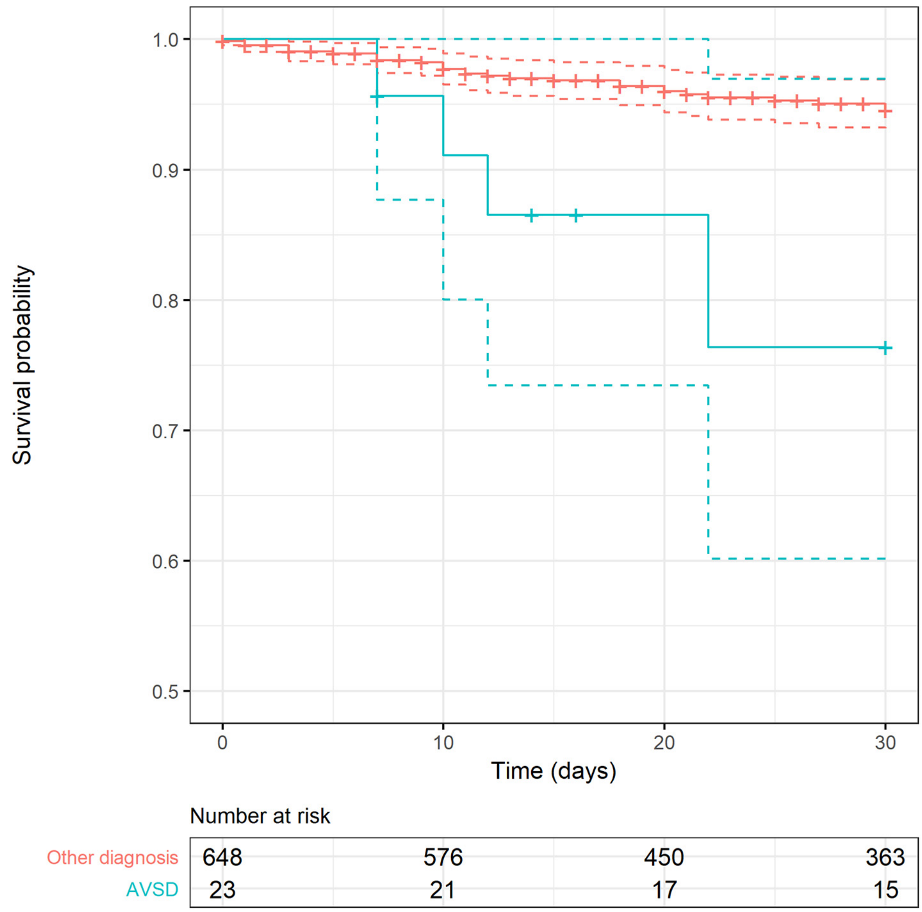
Kaplan–Meier analysis demonstrating overall survival according to the presence of staphylococcal infection. The dashed lines show the 95% confidence interval for the point estimate.

from the European Society of Cardiology and American Heart Association, which recommend prophylaxis for patients with prosthetic valves, cyanotic CHD or prosthetic intracardiac material with a residual shunt.[11,12] Third, despite the rise in staphylococcal IE in adults, streptococci remain the most common causative organism in patients with CHD. Fourth, there are identifiable predictive factors of adverse outcome in CHD patients, which include staphylococcal infection and specific congenital heart lesions.

Several smaller studies have analyzed the epidemiological aspects of IE in CHD populations. A number of risk factors for developing IE in children with CHD have been identified, including cyanosis, atrioventricular septal defects and left-sided lesions.[13] Recently, two series have reported outcomes from patients with CHD who have undergone transcatheter pulmonary valve replacement, finding that there is a significant ongoing risk of IE, and identifying an elevated post-deployment transvalvular gradient as a key risk factor for IE.[14,15] Following diagnosis, staphylococcal infection has been identified as a risk factor for mortality in children without pre-existing heart disease and adults, but this has not previously been reported in patients with CHD.[8,16] A rising incidence of staphylococcal IE has been reported in CHD patients in France and the UK, although our study demonstrates that streptococci remain the predominant organism.[17,18] In-hospital mortality from IE in CHD populations ranges from 1.9% - 9%, consistent with our findings.[18,19] In a recent Norwegian population study with long-term follow-up (mean 12.4 years), IE-related mortality in children or adolescents with severe CHD was 8%.[20]

The strengths of this study are that it provides data from a large, multicenter prospective observational cohort study and insights into a relatively rare and understudied population. Indeed, the size of our cohort has facilitated the first multivariable survival analysis in patients with

Figure 3



Kaplan–Meier analysis showing overall survival of patients with infective endocarditis and an underlying atrioventricular septal defect in comparison with other diagnoses. The dashed lines show the 95% confidence interval for the point estimate.

CHD. However, we also acknowledge several limitations. First, since local clinicians undertook data entry there are limitations in completeness, particularly concerning the stage of surgical repair for individual patients. As a result, in some cases it is not clear which were operated on or not, an important aspect when establishing risk of infective endocarditis. These missing data preclude an analysis of the role of indwelling prosthetic material or residual defects. Conduction of the study at tertiary congenital centers may have resulted in selection or referral bias. The length of stay may therefore reflect only the period spent in the tertiary center and overlook additional time in a local hospital before or after regional transfer. For pediatric patients, it is very unlikely that a tertiary referral center would not be involved in the patient's care, but some adult congenital patients may have been managed in district general hospitals and not enrolled into the study. Therefore, this study population may not be wholly representative of the entire UK congenital population and underreporting is likely. Further limitations in the data set preclude analysis of causative organisms, microbiological analysis of surgically explanted material, echocardiographic findings, the incidence of complications or surgical management. Data was missing for 11–13% of patients for the following fields: diagnosis, recent dental procedure, recent invasive procedure.

This study has several implications for future research. First, it emphasizes the value of prospective national or international registries for CHD, where large numbers of patients are required for statistical power. An important research priority is to define the incidence of IE over time in clearly defined populations with repaired and unrepaired CHD. Second, it highlights the importance of specific high-risk features in determining patient outcome. Assessing whether aggressive, early surgical treatment of CHD patients with staphylococcal disease improves outcome is an important question for future research. Further work is also required to clarify the role of invasive procedures as opposed to everyday bacteremia as a cause of IE.[21] In adults, recent case-crossover studies have suggested that invasive dental and medical procedures may be associated with increased risk of IE.[22,23] Although there are additional uncertainties surrounding the efficacy of antibiotic prophylaxis,[24] these studies suggest that invasive procedures expose CHD patients to an additional transient risk and prophylactic strategies may be appropriate. Identification of the causative organism for IE remains important both to ascertain the role of invasive procedures and health-care contact in the disease etiology, and for selection of the appropriate antibiotic strategy.

In summary, IE is an important complication of CHD that is associated with in-hospital mortality in approximately 1/15 cases. Streptococci remain the most common causative organism, and antecedent dental or medical procedures were undertaken in 11.0–27.4% in the 3 months before diagnosis. The presence of an atrioventricular septal defect or staphylococcal infection is associated with significantly increased risk of early mortality.

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Authorship

The authors are solely responsible for the design and conduct of this study, all study analyses, the drafting and editing of the paper and its final contents.

Conflicts of interests

None to declare.

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Appendix. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.05.014.

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