Endocarditis in children and adolescents with congenital heart defects: a Norwegian nationwide register-based cohort study

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ABSTRACT

Objectives Congenital heart defects (CHDs) are the most common birth defects worldwide and are an important cause of morbidity and early death. A significant number of deaths occur among patients with infections. CHDs predispose to the development of infective endocarditis (IE) and represent a risk factor for increased mortality due to IE. The aim of this study was to investigate the occurrence and outcomes of IE in children and adolescents with CHDs.

Methods Data on all children with CHD and IE born in Norway between 1994 and 2016 were retrieved from the Oslo University Hospital’s Clinical Registry for Congenital Heart Defects. Survivors were followed through 2016, and supplementary information was retrieved from medical records.

Results In this nationwide register-based cohort study, which included all 1 357 543 live births in Norway between 1994 and 2016, the incidence of IE according to the European Society of Cardiology diagnostic criteria was 2.2 per 10 000 person-years among children and adolescents with CHDs. The incidence was stable throughout the period. Most patients with IE had severe CHDs (75%) and had undergone open chest cardiac surgery or catheter-based cardiac interventions the last year before IE. IE-related mortality among children with CHDs and IE was 8% during the follow-up period (mean 12.4 years (±5.5 years)).

Conclusions The incidence of IE among children and adolescents with CHDs was higher than the reported incidence in the general population. IE was associated with severe CHDs and recent complex cardiac interventions, and had significant mortality.

INTRODUCTION

Infective endocarditis (IE) is a bacterial or fungal infection of the endocardium and/or heart valves that damages the endocardial tissue and/or valves.1 IE is infrequent in children and adolescents, but the current incidence is not exactly known. We recently reported a low frequency of IE in children without pre-existing heart disease in Norway.2 However, most children and adolescents with IE have an identifiable risk factor, and congenital heart defects (CHDs) represent the major risk factor for IE today.3–5

CHDs are the most common birth defects worldwide, and affect approximately 1 per 100 live births.6–8 Survival of patients with CHDs has improved, and the population of children and adolescents with CHDs is expanding.7 9–12 Despite the improved survival, CHDs still represent an important cause of morbidity and death at young ages.11 13–15 A significant number of deaths occur among patients with infections.11 16 The previously reported incidence of IE in patients with CHDs is 15–140 times higher than that in the general population,3 17–19 and CHDs also represent an important risk factor for increased mortality and complications in patients with IE.5

Antimicrobial prophylaxis is warranted before selected high-risk procedures in patients with increased risk of IE, but the evidence of a treatment benefit is weak.1 20 The 2009 European Society of Cardiology (ESC) guidelines for the prevention, diagnosis and treatment of IE limit antibiotic prophylaxis to patients with the highest risk and focused on healthcare-associated IE. The consequences of these changes for the incidence and outcomes of IE are not known, but the same policy was recommended in the 2015 ESC guidelines.1

Norwegian health registers provide a unique opportunity to conduct nationwide population-based studies. The aims of this study were to investigate the occurrence of IE according to the ESC diagnostic criteria, in children and adolescents...
with CHDs who were born in Norway from 1994 to 2016, and to characterise their heart defects, previous treatments, diagnostic features and outcomes of IE.

METHODS

Data sources
The number of births in Norway between 1994 and 2016 was retrieved from the Norwegian National Population Registry. Individual medical information about the children with CHDs and IE who were born in this period was retrieved from the Oslo University Hospital’s Clinical Registry for Congenital Heart Defects. Oslo University Hospital serves as a national centre for children and adolescents with CHDs in Norway. Norway has no registry covering all patients with CHDs, but children and adolescents with CHDs and suspected IE are routinely referred from local hospitals to Oslo University Hospital. Registration in the Oslo University Hospital’s Clinical Registry for Congenital Heart Defects is mandatory for all patients with CHDs examined at the hospital. Detailed description of the registry has been published previously. Potential IE cases were identified by searching specific diagnostic codes (International Classification of Diseases (ICD-9) 421.0–421.9, 424.9; ICD-10 I33.0–I33.9, I38, I39; and van Mierop 94219) in the registry. Medical records, imaging, laboratory findings and death certificates were reviewed manually by a group of three experienced cardiologists for all of the included patients.

Infective endocarditis
IE was defined as a bacterial or fungal infection of the endocardium and/or heart valves, and for all patients with a diagnosis of IE, the clinical findings and symptoms were evaluated against the ESC 2015 diagnostic criteria.

Classification of CHDs
CHDs were defined as structural abnormalities of the heart or intrathoracic vessels with functional or potentially functional significance. Children with isolated cardiomyopathies and primary arrhythmias were not included. CHDs were classified as severe (transposition of the great arteries, tetralogy of Fallot, double outlet right ventricle, truncus arteriosus, interrupted aortic arch, atroventricular septal defects, anomalous pulmonary venous return, hypoplastic left heart syndrome, coarctation of the aorta, valvarular aortic stenosis, pulmonary valve atresia, tricuspid valve atresia, Ebstein’s anomaly and other complex defects) or non-severe (atrial septal defects, ventricular septal defects (VSDs), minor valve malformation, venous malformations, pulmonary valve stenosis and isolated patent ductus arteriosus).

Study population
All 1 357 543 live births in Norway from 1 January 1994 to 31 December 2016 were registered in the National Population Registry of Norway and comprised the background population. Based on the birth prevalence and mortality of CHD in Norway from 1994 to 2009, we estimated that approximately 16 300 children were born with CHDs in the period from 1994 to 2016, with a total follow-up time (0–18 years old) of approximately 164 000 person-years. The Norwegian population of children with CHDs born 1994–2009 is extensively described previously in the research project Congenital Heart Defects in Norway; compared with the general population, more children with CHDs were girls (50.1% vs 48.6%, P=0.01), were born preterm (15.9% vs 6.5%, P<0.001) and were small for gestational age (15.6% vs 8.8%, P<0.001). The proportion classified as severe CHD was 23.7%, the loss of follow-up was <1%, and the 1-year mortality during the period was 6.0%. The ends of the follow-ups in this study were death, the 18th birthday or 31 December 2016 (ie, the end of the study) depending on which occurred first. Children and adolescents with CHDs and IE born between 1994 and 2016 were identified in the Oslo University Hospital’s Clinical Registry for Congenital Heart Defects.

Statistical analysis
Continuous variables are presented as average ±SD or median (lower and upper quartiles). The estimated rates of IE in children with CHDs refer to the recorded numbers of IE divided by the estimated total number of observed person-years, and are expressed per 10 000 person-years. Time trends were analysed (log-linear model) using Joinpoint Regression Program (V4.0; SEER software, National Cancer Institute, USA). Other statistical analyses were performed using STATA V14.

RESULTS

Incidence
Among the 1 357 543 live births in Norway from 1994 to 2016, the combination of an IE diagnosis and CHD diagnosis before 18 years of age was identified in 39 patients during the 23-year period. A total of 36 patients met the ESC 2015 diagnostic criteria of IE. The estimated rate of IE among patients 0–18 years old with CHDs was 2.2 per 10 000 person-years. The number of IE was 0–5 per year, and we found no time trend changes in the incidence of IE in Norway from 1994 to 2016.

CHDs and risk factors
During the study period, IE was diagnosed in 25 (69%) boys and 11 girls with CHD. The median age at the time of IE was 3.1 (lower quartile 0.7, upper quartile 9.9) years (figure 1A). Most patients had a severe CHD (n=27, 75%). The main CHD diagnoses are listed in table 1. No patients had previous IE. A total of 27 children (75%) had undergone open chest cardiac surgery before IE, and of the unoperated, two children had undergone cardiac catheter interventions. The majority of these patients had undergone multiple cardiac interventions before IE (>1 procedure in 16 patients (55%)). Prosthetic materials were used for CHD repairs in 96% (n=26) of patients who had undergone cardiac surgery before IE. In most patients, the prosthetic materials used were patches, shunts or conduits, but one child had a pacemaker and another had an implanted mechanical heart valve. The median age at the first cardiac intervention was 28 (lower quartile 7, upper quartile 361) days, and the median age at the last cardiac intervention before IE was 207 (lower quartile 16, upper quartile 981) days. Catheter-based interventions were the last cardiac procedure in 4 of the 29 children who underwent cardiac interventions before IE (one Amplatzer Muscular VSD Occluder, one aortic valve balloon valvulotomy, one right ventricular outflow tract stent and one Melody Transcatheter Pulmonary Valve; table 1). The median time from the last cardiac intervention (surgery or catheter-based intervention) to IE was 77 (lower quartile 31, upper quartile 902) days (figure 1B). Nearly half of the cases of IE were diagnosed within 60 days after cardiac interventions (n=14) in patients with cardiac interventions before IE, and in 67% (n=20) of the cases within 1 year. Only six patients with non-severe CHDs without cardiac surgery/catheter-based interventions were registered with IE in Norway during the study period. None of the patients with IE had body piercings or tattoos. 

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tattoos, and no preceding dental procedures with manipulation of the gingival or periapical region of the teeth or perforation of the oral mucosa were recorded.

**Diagnostic features**

Fever was the most frequent presenting IE feature (86%, n=31; [table 2]). Embolic phenomena were recorded in three (8%) patients. Blood cultures were positive in 30 (83%) patients. *Viridans streptococci* (33%, n=12) and *Staphylococcus aureus* (22%, n=8) were the most frequently detected micro-organisms in the blood culture-positive IEs. Echocardiography was performed in all patients. Vegetations were found in 22 patients (61%), abscesses were found in 2 patients, and 1 patient had a new-onset valvular regurgitation. Among those with echocardiographic findings, the aortic valve, pulmonary valve/graft, mitral valve and tricuspid valve were affected in seven, five, four and two patients, respectively. In one child, IE was related to pacemaker leads; in one child IE was related to a VSD occluder, and in three patients IE was related to surgically implanted shunts. Eleven patients (31%) had no echocardiographic findings suggestive of IE.

**Outcomes**

All children with IE were treated with antibiotics. Thirteen (38%) patients underwent cardiac surgery as part of the IE treatment. Mechanical heart valves were implanted in two cases. Three patients died (8%) of multiple organ failure related to IE. The mean study follow-up time was 12.4 years (±5.5 years). None of the patients experienced recurrent IEs during this period.

**DISCUSSION**

In this cohort study, which included all live births in Norway between 1994 and 2016, the incidence of IE according to the ESC diagnostic criteria, among children and adolescents (0–18 years old) with CHDs, was higher than the incidence of IE in the general population. The IE incidence was stable throughout the period. Most patients with IE had severe CHDs and had undergone open chest cardiac surgery or a catheter-based cardiac intervention the last year before IE. The IE-related mortality was 8% during the follow-up period.

As highlighted in the last ESC guidelines for IE, our knowledge of IE in patients with CHDs is very limited. There are few systematic studies of IE in patients with CHDs, and selection bias associated with the studies from highly specialised centres hampers universal application. New knowledge of the incidence, risk factors, symptoms, complications and outcomes is essential for improved prevention and therapy of IE in children and adolescents with CHDs. This Norwegian study of IE and CHDs...
The 2009 and 2015 ESC guidelines for the prevention, diagnosis and treatment of IE limit antibiotic prophylaxis to patients with the highest risk (those with prosthetic valves, previous episodes of IE, cyanotic CHDs and CHDs repaired with a prosthetic material up to 6 months after the procedure or lifelong if a residual shunt or valvular regurgitation remains). The occurrence of IE among children and adolescents with CHDs was stable in Norway in the period from 1994 to 2016. Similarly, Toyoda et al recently described a stable incidence of IE in the general populations in California and New York State from 1998 to 2013. None of these studies indicated a negative effect of the changes in the guidelines on the incidence of IE.

The highest risk of IE has been observed in patients with prosthetic materials from previous cardiac surgery or catheter-based interventions, and in children aged less than 3 years or who have undergone cardiac surgery early in life. CHDs often consist of multiple cardiac lesions, each contributing to the total risk of IE. These findings are supported by our study, as most of the patients with CHD with IE had severe defects and had undergone complex cardiac surgery early in life. There are still controversies about prophylactic antibiotic treatment during cardiac surgery. In Norway, perioperative and postoperative prophylaxis was routinely given all through the period. Our data do not allow for an assessment of the effect on the occurrence of IE.

We previously reported that 95% of children with VSDs are left without surgical or catheter-based closure of the defect, and the numbers of persistent shunts at the atrial and ductal levels are also large. In this study, we registered only four cases of IE in patients with untreated simple left-to-right shunts, which indicates a low risk of endocarditis in these groups.

The risks of IE associated to the growing societal trends of cosmetic tattooing and piercing are not known. None of the patients with IE in this study had body tattoos or piercings, but most of the patients were children, and no conclusions can be drawn based on this study.

The diagnosis of IE is challenging. IE may present as an acute, rapidly progressive infection, but it may also present as a subacute or chronic disease with low-grade fever and non-specific symptoms that may mislead or confuse the initial assessment. The diagnosis of IE is based on the Duke criteria, which was last modified by the ESC in 2015, and requires history, clinical examination, blood culture, laboratory results and echocardiography. The symptoms and basis for the diagnoses in patients with CHDs do not differ from IE in general. A variety of microorganisms can cause IE, and Streptococci and Staphylococci are the most common pathogens also in children with CHDs. In the present study, the percentage of patients with blood culture-negative IE was 17%, which is lower than previously presented in adult patients. The possible reasons for negative blood cultures may include early administration of antimicrobial agents, infections with highly fastidious bacteria, or IE caused by virus or fungi. Positive blood culture is one of two major criteria for the diagnosis of IE, and only patients who fulfil the ESC diagnostic criteria were included in this study. High attention to possible IE in patients with CHDs and diffuse symptoms may also explain the low proportion of patients with negative blood cultures. However, the diagnosis of IE is difficult and often made late, which highlights the need to consider the diagnosis of IE in any patient with a CHD who presents with fever or other signs of infection.

Despite improvements in diagnostics and management, IE remains associated with a significant morbidity and mortality. Earlier studies have described an overall IE mortality rate of approximately 5% in children. This study presents a mortality rate of 8% and supports the notion that CHDs still represent a risk factor for mortality and complications of IE.

The main strengths of the present study are the large and unselected nationwide population, and a comprehensive follow-up. Some study limitations must be noted. The incidence of CHD in Norway was less precisely defined for the period of 2009–2016, which may have affected the reported incidence of endocarditis. However, because of the rare occurrence of IE, potential errors in the estimates have limited consequences. We may also lack information on IE in some children and adolescents who were never examined at Oslo University Hospital. However, all cases with suspected IE in patients with CHDs are routinely referred from local hospitals for specialist evaluation, and we believe that the number of potentially missed cases is minimal. This study
only included cases that fulfilled the ESC criteria of IE, and patients with culture-negative IE may be under-represented. This is a diagnostic grey-zone, and we believe that strictly sticking to the criteria strengthens the reliability of our findings even if they represent a minimum prevalence. Our data do not allow for precise estimates of the risk factors for IE or relative risks of IE in children with different kinds of CHDs. Further and differently designed studies are needed to provide this information. It should also be emphasised that the follow-up time was 0 to 18 years from birth, and the risks and outcomes of IE in adults with CHDs likely differ from the risks and outcomes in the youths.

In conclusion, the incidence of IE among children and adolescents with CHDs in Norway in the period 1994–2016 was higher than the reported incidence in the general population. Despite the restrictions against antibiotic prophylaxis to patients with the highest risk in 2009, the incidence of IE was stable throughout the period. IE was associated with severe CHDs and recent complex cardiac interventions, and had significant mortality. In our view, it is still essential to underline the importance of adequate prevention, early detection and rapid treatment of IE in many patients with CHDs.

Contributors JJ contributed to concept and design, acquisition, analysis and interpretation of data, drafting and revising the manuscript, approval of the manuscript, and is accountable for all aspects of the work. KH contributed to acquisition and interpretation of data, revising the manuscript, approval of the manuscript and is accountable for all aspects of the work. HH contributed to concept and design, acquisition and interpretation of data, revising the manuscript, approval of the manuscript and is accountable for all aspects of the work.

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Competing interests None declared.

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