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ORIGINAL RESEARCH ARTICLE

Infective endocarditis in adults with congenital heart disease remains a lethal disease

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ABSTRACT

Objective Infective endocarditis (IE) is associated with significant morbidity and mortality. Patients with adult congenital heart disease (ACHD) have an increased risk of developing IE. The aim of this study is to describe the incidence, predictors of outcome and mortality associated with IE in ACHD in a contemporary cohort.

Methods All episodes of IE in adults with congenital heart disease referred to our tertiary centre between 1999 and 2013 were included in the study. Patients were identified from the hospital database. The diagnosis of endocarditis was established according to the modified Duke criteria. The primary endpoint of the study was endocarditis-associated mortality.

Results There were 164 episodes of IE in 144 patients (male 102, 70.8%). Mean age at presentation was 32.3±22.7 years. Out of these, 43% had a simple, 23% a moderate and 32% a complex lesion. It was at least the second bout of IE in 37 episodes (23%). A predisposing event could be identified in only 26.2% of episodes. Surgical intervention during the same admission was performed in 61 episodes (37.2%). During a median follow-up of 6.7 years (IQR 2.9–11.4), 28 (19.4%) patients died. Out of these, 10 deaths were related to IE (IE mortality 6.9%). On unvariate regression analysis, the development of an abscess (OR: 7.23; 95% CI 1.81 to 28.94, p<0.01) and age (OR: 1.05; 95% CI 1.01 to 1.10, p=0.03) were the only predictors of IE-associated mortality. There was no increase in IE cases at our centre during the period of the study.

Conclusions IE-associated morbidity and mortality in a contemporary cohort of ACHD patients is still high in the current era.

INTRODUCTION

The risk of infective endocarditis (IE) in patients with adult congenital heart disease (ACHD) is substantially higher than in the general population.[1] The yearly incidence of IE in the general population is between 3 and 7 per 100 000 person-years,[2] while in ACHD, the incidence is around 1.1 per 1000 patient-years with a marked variation between different types of CHD.[3] Therefore, IE accounts for up to 4% of admissions to a tertiary ACHD centre, with an associated mortality of approximately 4%.[4] In the past, many ACHD patients received antibiotic prophylaxis for IE when undergoing invasive investigations or procedures, especially dentistry. However, the lack of any convincing evidence in support of antibiotic prophylaxis on efficacy and risk–benefit ratios led to a major shift in practice in 2008 when IE prophylaxis was abolished for most or all patients, depending on national and international guidelines.[5–8] The impact of this shift in practice on the clinical course of IE in the ACHD population remains unknown. Furthermore, current data regarding the diagnosis and outcome of IE in ACHD is lacking. Therefore, the aim of this study was to investigate the morbidity and mortality associated with IE in a contemporary cohort of patients with ACHD who are cared for in a large tertiary ACHD centre and to identify predictors of outcome.

METHODS

In this retrospective study, all documented episodes of IE treated at the Royal Brompton Adult Congenital Heart Centre, London, UK, between 1999 and 2013 were included. Generally, these were adult patients with a congenital heart defect including bicuspid aortic valves.

The primary endpoint of the study was endocarditis-associated mortality. Deaths were identified from the hospital database, linked to the Office of National Statistics, which registers all UK deaths. Information on the cause of death was retrieved, when possible, from the medical records. As this was a retrospective analysis of data collected for routine clinical care and administrative purposes, individual informed consent was not required (UK National Research Ethics Service guidance). The study was locally registered and approved.

Clinical data

Demographic data and information on medical and surgical history were retrieved for all patients from hospital records. Complexity of congenital heart disease was graded according to the Bethesda classification.[9] The diagnosis of endocarditis was established according to the modified Duke criteria.[10] Redo sternotomy was defined as a sternotomy performed after 15 days from previous sternotomy, thus excluding reoperation for postoperative bleeding. Arrhythmic events include any type of sustained supraventricular or ventricular arrhythmia requiring treatment.

Timing of surgery was classified according to the most recent European guidelines: emergency

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surgery: surgery performed within 24 hours; urgent surgery: within a few days; elective surgery: after at least 1–2 weeks of antibiotic therapy.[5]

Statistical analysis

Statistical analyses were performed using MedCalc V.12.3.0.0 (MedCalc Software, Mariakerke, Belgium) and SPSS V.15.0 (SPSS, Chicago, Illinois, USA). Continuous variables are presented as mean±SD or median (IQR), whereas categorical variables are presented as number (percentage). Logistic regression analysis was used to assess the association between variables and IE mortality.

To assess the possible association between the publication of the new endocarditis guidelines and the incidence of endocarditis seen at our centre, we correlated time with the absolute rate and the endocarditis rate corrected for the number of patients under follow-up. In addition, an interaction term (pre-2009/post-2009) was used in the regression analysis to assess whether the slope of the association differed before and after guideline publication.

All tests were performed two sided, and for all analyses, a p value<0.05 was considered statistically significant.

RESULTS

Population and initial presentation

We identified 144 patients (male n=102 (70.8%)) with 164 episodes of IE during the study period. Mean age at presentation was 32.3±22.7 years. Out of these, 43% had a simple, 23% a moderate and 32% a complex lesion, while 2% could not be classified according to the Bethesda criteria. The number of IE episodes according to main congenital heart lesion is described in table 1. Left ventricular outflow tract disease included four episodes in patients with aortic stenosis, 32 episodes in patients with bicuspid aortic valve, three episodes in patients with a coarctation of the aorta in combination with a bicuspid aortic valve, one episode in a patient with a coarctation of the aorta and four episodes in patients with other left ventricular outflow tract obstruction.

In 100 (61.0%) IE episodes, history of at least one previous open heart surgery was known, whereas in 86 (52.4%), prosthetic material was present.

Recurrent endocarditis was common: 37 (23%) of 164 cases had previous IE episodes: in one case it was the sixth episode, whereas in another three cases, it was the fifth episode. Renal function was abnormal in 15 episodes (9.1%), whereas at least one liver marker was abnormal in 51 episodes (31.1%). Twenty patients (13.9%) were on therapy with warfarin, 32 patients (22.2%) had a history of smoking and in 4 (2.8%) a diagnosis of diabetes mellitus was present.

A predisposing event likely to have caused IE was identified in 43 episodes (26.2%). Out of these, previous dental treatment was the most common event (27.9%); other predisposing events included skin infection (23.3%), recent surgical or interventional cardiac treatment (14.0%) and gynaecological procedures (4.7%). Recent history of upper respiratory tract infection was present in four episodes (9.3%), whereas in another 10 (23.3%), a recent musculoskeletal infection, gastroenteritis or urinary tract infection was reported. In 25 out of 43 (58.1%) episodes with a predisposing event, prophylactic antibiotic treatment had been administered; 7 out of 12 patients who had received invasive dental treatment had concomitant antibiotic prophylaxis.

At least one positive blood culture report or PCR was available in 136 (83.0%) episodes. They were reported negative in 21 episodes and were unavailable in 7. Streptococci were found in 69 (50.7%), *Staphylococcus aureus* in 26 (19.1%), coagulase-negative Staphylococci in 17 (12.5%) and Gram-negative rod bacteria in nine episodes (6.6%), half of whom belong to the haemophilous species. Gram-positive bacteria could be detected in eight episodes, enterococci in five and fungi in 2.

Vegetations were detected in 138 (84.1%) episodes and in 57 (41.3%) of these a transoesophageal echocardiogram was required in order to confirm presence of a mass or to investigate multiple valve involvement. Presumably active masses involving more than one heart structure were detected in 27 (19.6%) episodes.

The most frequent location of a presumed endocarditic mass/vegetation was the left ventricular outflow tract (39.1%, n=54, prosthetic materials in 40.7%, n=22). The pulmonary valve was infected in 44 (31.9%) episodes (prosthetic in 37 episodes (84.1%), native in 7 (15.9%). The right or left atrioventricular valves were affected in 15 (10.9%) and 17 episodes (12.3%) respectively, whereas in two episodes (1.4%) both were affected. Evidence of IE on a ventricular septal defect was present in 22 (15.9%) episodes; in 11 out of these, it was associated with infections of either the tricuspid valve or the right ventricular outflow tract. In 13 episodes (9.4%), other cardiovascular structures were involved, including pacemaker leads, a common atrioventricular valve (in a patient with complete atrioventricular septal defect), venous baffles and previous coarctation repaired area.

Table 1 Number of IE episodes according to main congenital heart lesion

Diagnosis	Number of episodes (%)
Left ventricular outflow tract disease	44 (26.8)
Shunt	42 (25.6)
Tetralogy of Fallot/pulmonary atresia	36 (22.0)
TGA	20 (12.2)
Complex CHD	7 (4.3)
Single ventricle physiology	6 (3.7)
Mitral valve disease	3 (1.8)
Miscellaneous	6 (3.7)

Complex CHD: Eisenmenger syndrome, truncus arteriosus, Ebstein's anomaly; Miscellaneous: double chambered right ventricle, sinus of Valsalva aneurysm, Marfan syndrome; Shunts: ventricular septal defect, patent ductus arteriosus, atrioventricular septal defect; TGA: transposition of the great arteries and congenitally corrected transposition of the great arteries.
CHD, congenital heart disease; IE, infective endocarditis.

Management and outcome

All patients admitted or referred to our centre were started on empiric antibiotic therapy, if not already initiated in the admitting district hospital, until the blood culture results became available (figure 1). Data about the therapy duration were available in 116 episodes. The median duration of antibiotic therapy was 42 (range 2–201) days.

Surgery at the same admission was performed in 61 episodes (37.2%). In 7 (11.5%) of these episodes, surgery was performed as an emergency procedure due to acute heart failure. In 22 (36.1%) surgery was performed as an urgent procedure due to acute severe valvular regurgitation (n=9), presence of abscess (n=5), embolic events (n=3), significant valve stenosis (n=3) and no response to medical therapy (n=2). Surgery was performed as an elective procedure in 32 (52.5%) of these episodes during the same admission after a median time from hospital admission of 16 (IQR 11–28) days. The most frequent reason for an

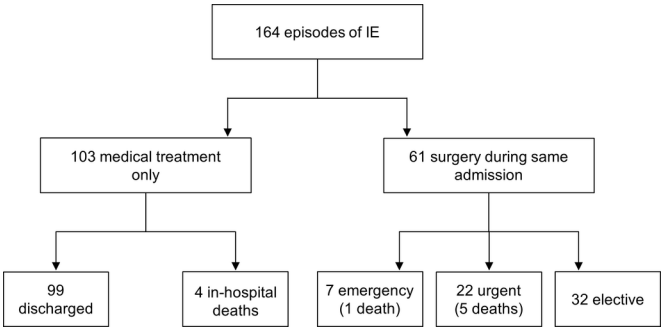

Figure 1 Flow chart of patient management and outcome. IE, infective endocarditis.

elective operation during the same admission was significant valvular dysfunction (n=21), in the remaining patients embolic events, no response to medical therapy or other complications were present.

Approximately, half of the patients in the emergency (3 out of 7) and urgent (12 out of 22) surgery groups developed postoperative complications, including arrhythmias, heart failure, liver or renal dysfunction or slow respiratory weaning. Six patients who underwent same admission surgery died, one who underwent emergency surgery and five who underwent urgent surgery. The cause of death was heart failure in five patients and uncontrolled sepsis in 1.

Postdischarge, at a median time of 195 (IQR 96–221) days, 16 patients were operated for complications of IE that did not require surgery during the initial admission, mainly for valvular dysfunction

Mortality

During a mean follow-up of 10.1±19.0 years, 28 (19.4%) patients died (see online supplementary table 1). Out of these, 10 deaths occurred in-hospital and were related to IE (in-hospital mortality 6.9%).

On univariate analysis, significant predictors of in-hospital mortality (table 2) were the development of an abscess (OR: 7.23; 95%CI 1.81 to 28.94, p<0.01) and age at presentation (OR: 1.05; 95%CI 1.01 to 1.10, p=0.03). The following parameters were also tested but were unrelated to in-hospital mortality: gender, complexity of congenital heart defect, emboli during IE, *S. aureus* infection, presence of prosthetic material and previous episode of IE (table 2). On multivariate analysis considering the significant predictor variables of the univariate analysis, only development of an abscess (OR: 5.33; 95%CI: 1.27 to 22.40, p=0.02) remained as a significant predictor (Hosmer & Lemeshow test p=0.62, area under the receiver operating characteristics curve 0.78).

Table 2 Baseline predictors of in-hospital mortality

	Univariate	
	OR (95% CI)	p
Age (years)	1.05 (1.01 to 1.10)	0.03
Gender	1.09 (0.27 to 4.41)	0.90
Bethesda complexity of CHD	0.98 (0.59 to 1.64)	0.95
Emboli	3.28 (0.86 to 12.45)	0.08
Staphylococcus aureus infection	1.29 (0.26 to 6.44)	0.76
Presence of prosthetic material	2.22 (0.55 to 8.88)	0.26
Previous IE	0.36 (0.04 to 2.97)	0.35
Cyanosis	1.58 (0.31 to 7.97)	0.58
Abscess	7.23 (1.81 to 28.94)	<0.01

CHD, congenital heart defect; IE, infective endocarditis.

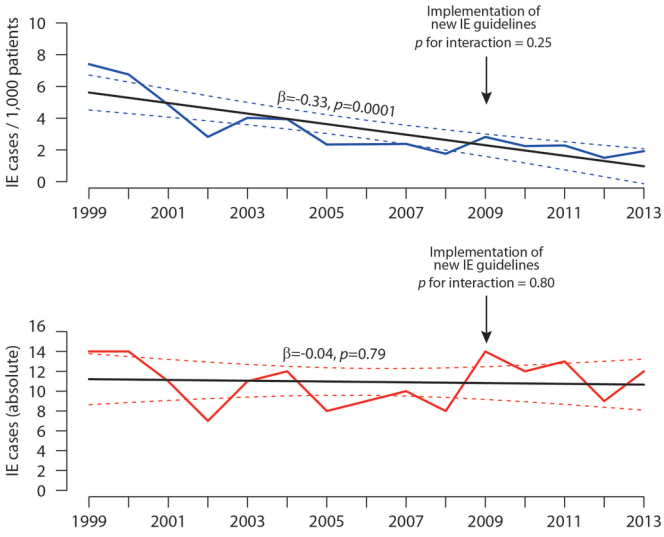

Figure 2 Incidence (A) and absolute number (B) of endocarditis episodes at the Adult Congenital Heart Unit of the Royal Brompton Hospital from 1999 to 2013. IE, infective endocarditis.

The number of patients treated for IE at our centre did not increase in the period between 1999 and 2013 (figure 2). The change of guidelines seemed not to have an impact on the incidence of IE at our centre (figure 2).

DISCUSSION

In this study of a contemporary cohort of patients with ACHD treated in a large tertiary ACHD centre, IE is still associated with significant morbidity and mortality. Surgery was often necessary, and the in-hospital mortality was 6.9%.

Surgical treatment may be necessary in up to 50% of cases with IE in the general population.[11] In our study, surgery was necessary in 37% of the episodes during the same admission, which is higher than previously reported figures in ACHD.[4] One reason could be that our case mix is getting more complex, making surgery more likely. Furthermore, surgical techniques have evolved with multiple reoperations, use of prosthetic material and extensive repair as possible substrates for IE necessitating surgical intervention. This clearly underscores the need to transfer promptly patients with ACHD with suspected IE to a tertiary centre and on arrival inform the surgical team of the potential need for same admission surgery.

Streptococci were the most frequent causative microorganisms identified in our study, and there is no significant difference in the type of causative microorganisms compared with a study from our institution covering the period from 1983 to 1996 or studies from other institutions.[4 12] While neither a French nor a US study reported an increase in the number of IE cases caused by Streptococci after the change of guidelines for antibiotic prophylaxis, there was a worrisome increase in the incidence of cases caused by Staphylococci in the study by Duval and colleagues.[12 13] Reassuringly, studies in patients with CHD observed no increase in the number of Staphylococci spp.-associated cases of IE over time.[14 15]

Mortality related to IE, while lower than in the general population, remains substantial, with a mortality of 6.9% in our cohort.[11 12] A previous paper on ACHD patients with IE reported

a mortality of 8%,[15] whereas in an older study from our institution, mortality was 4%.[4] Reasons for the lower mortality from IE in ACHD compared with other cohorts may be the younger age of patients with ACHD and the higher prevalence of right-sided IE. Oliver *et al* reported in a study of all patients with IE presenting to a French referral centre an in-hospital mortality of 10.4% for patients younger than 65 years, 13.3 .% for patients between 65 and 80 years and 15.7% in patients over 80 years.[16] Furthermore, in a Swedish study of all patients with IE referred to Huddinge University Hospital, patients with right-sided IE (all being injecting drug users (IDUs)) had a better outcome than patients with left-sided IE (0% in-hospital mortality vs 13% in all patients with left-sided IE vs 17.4% of IDU patients with left-sided IE).[17] Additionally, it is also increasingly recognised that patients with IE treated in centres with established 'endocarditis teams', that is, multidisciplinary teams experienced in the medical and surgical management of IE, have significantly better outcomes.[5] ACHD patients followed in tertiary specialist centres have long benefitted from such expertise, as all established ACHD multidisciplinary teams can be described as 'endocarditis teams'. Moreover, awareness of the risk of IE is higher in patients with ACHD and their treating physicians, probably leading to earlier diagnosis and perhaps a more favourable outcome.

UK National endocarditis guidelines[18] differ substantially to international guidelines[5–8] with regards to antibiotic prophylaxis for endocarditis. European Society of Cardiology (ESC) and American Heart Association (AHA) guidelines have substantially restricted endocarditis prophylaxis to 'high-risk' patients. UK guidelines, however, recommend that no patient should receive endocarditis prophylaxis, based on the lack of strong evidence of efficacy. In our centre, a change in practice occurred in 2009, when all ACHD physicians adopted ESC rather than national guidance. Despite reducing numbers of patients with ACHD advised to receive IE prophylaxis, our practice of informing all patients with ACHD about the risk of IE, precautions to take and ways of identifying IE early continued. All patients were reminded to maintain good dental and skin hygiene, visit their dentist regularly, seek treatment for recurrent skin infections (eg, acne) and avoid tattoos or piercings. Our practice may have contributed to the result that the incidence of IE seems to be stable over the years in our centre. This is in accordance with other international studies from France and the USA.[12 13] While no increase in the incidence of IE was reported in the latter studies, a recent study by Dayer *et al* reported a significant increase in the incidence of IE cases for the UK with the fall in prescriptions of antibiotic prophylaxis after the implementation of the national guidelines.[19] The results of this study raise concerns and have triggered careful re-examination of the UK national guidelines.

In our study, a predisposing event could be identified only in 43 episodes (26.2%). This is in accordance with the results of a German study of IE in congenital heart disease, in which only 30.8% of episodes had an identifiable predisposing event.[20] The fact that patients had received prophylactic antibiotics in 25 out of these 43 episodes in our study and then still went on to develop IE may serve as an argument against strict rules for antibiotic prophylaxis.

A major limitation of our study is its retrospective design. Furthermore, we cannot exclude referral bias influencing our results, since our hospital is a tertiary referral centre. One could speculate that IE cases in ACHD patients with simple defects and a 'mild' clinical course may have been treated in local hospitals, while more complex cases or cases with severe presentation of IE are more likely to be referred and transferred to us. However, this contradicts the advice to all our patients that if IE is suspected, we should be contacted and patients transferred to us as soon as possible. In addition, due to the small number of events, our sample size may not be adequate to provide definite conclusions about the effect of guideline changes on the incidence of IE in ACHD.

In conclusion, IE-associated morbidity and mortality remains high. IE in ACHD warrants diagnostic vigilance and early referral to a tertiary ACHD centre with surgical facilities. Despite optimal management, a life-long risk of developing IE persists. Prompt referral to an expert centre with on-site surgical facilities is paramount to minimise the considerable morbidity and mortality.

Key messages

What is already known about this subject?

- Patients with adult congenital heart disease (ACHD) have an increased risk of developing infective endocarditis (IE), which is associated with significant morbidity and mortality in historic cohorts.

What does this study add?

- In this contemporary cohort, there were 164 episodes of IE in 144 patients. Mean age at presentation was 32.3±22.7 years. Out of these, 43% had a simple, 23% a moderate and 32% a complex lesion. Surgical intervention during the same admission was performed in 61 episodes (37.2%). During a median follow-up of 6.7 years (IQR 2.9–11.4), 28 (19.4%) patients died. Out of these, 10 deaths were related to IE (in-hospital mortality 6.9%). On univariate regression analysis, the development of an abscess and age were the only predictors of IE-associated mortality.

How might this impact on clinical practice?

- This study emphasises that IE even in the current era is still associated with significant morbidity and mortality in ACHD. Early diagnosis and therapy is very important.

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Competing interests None declared.

Patient consent As this was a retrospective analysis of data collected for routine clinical care and administrative purposes, individual informed consent was not required (UK National Research Ethics Service guidance).

Ethics approval The study was locally registered and approved.

Provenance and peer review Not commissioned; externally peer reviewed.

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