European Journal of Pediatrics (2021) 180:3089–3100
https://doi.org/10.1007/s00431-021-04062-7

REVIEW

Infective endocarditis in paediatric population

Loay Eleyan[1] · Ameer Ahmed Khan[1] · Gledisa Musollari[2] · Ashwini Suresh Chandiramani[3] · Simran Shaikh[4] · Ahmad Salha[4] · Abdulla Tarmahomed[5] · Amer Harky[6,7]

Received: 7 March 2021 / Revised: 26 March 2021 / Accepted: 4 April 2021 / Published online: 14 April 2021

Abstract

Infective endocarditis is very uncommon in children; however, when it does arise, it can lead to severe consequences. The biggest risk factor for paediatric infective endocarditis today is underlying congenital heart defects. The most common causative organisms are *Staphylococcus aureus* and the viridans group of streptococci. The spectrum of symptoms varies widely in children and this produces difficulty in the diagnosis of infective endocarditis. Infective endocarditis in children is reliant on the modified Duke criteria. The use of blood cultures remains the most effective microbiological test for pathogen identification. However, in blood culture–negative infective endocarditis, serology testing and IgG titres are more effective for diagnosis. Imaging techniques used include echocardiograms, computed tomography and positron emission tomography. Biomarkers utilised in diagnosis are C-reactive protein, with recent literature reviewing the use of interleukin-15 and C-C motif chemokine ligand for reliable risk prediction. The American Heart Association (AHA) and European Society of Cardiology (ESC) guidelines have been compared to describe the differences in the approach to infective endocarditis in children. Medical intervention involves the use of antimicrobial treatment and surgical interventions include the repair and replacement of cardiac valves. Quality of life is highly likely to improve from surgical intervention.

Conclusion: Over the past decades, there have been great advancements in clinical practice to improve outcomes in patients with infective endocarditis. Nonetheless, further work is required to better investigative and manage such high risk cohort.

What is Known:
- *The current diagnostic techniques including 'Duke's criteria' for paediatric infective endocarditis diagnosis*
- *The current management guidelines utilised for paediatric infective endocarditis*

What is New:
- *The long-term outcomes of patients that underwent medical and surgical intervention*
- *The quality of life of paediatric patients that underwent medical and surgical intervention*

Keywords Cardiac valves · Duke's criteria · Empirical antibiotic therapy · Valve replacement · Valve repair

Communicated by Peter de Winte

✉ Amer Harky
amer.harky@lhch.nhs.uk

Loay Eleyan
Loayeleyan@gmail.com

Ameer Ahmed Khan
hlakhan8@liverpool.ac.uk

Gledisa Musollari
Gm2216@ic.ac.uk

Ashwini Suresh Chandiramani
ashwinii26c@gmail.com

Simran Shaikh
m1602122@sgul.ac.uk

Ahmad Salha
m1500889@sgul.ac.uk

Abdulla Tarmahomed
atarmahomed@nhs.net

Extended author information available on the last page of the article

Introduction

Paediatric infective endocarditis (IE) remains a complex disease even though there have been strides in the diagnostic techniques and management approaches over the past few decades [1]. IE is linked with a significant degree of morbidity and mortality [2]. The number of cases of IE in children, although rare, has been increasing in recent years [2]. IE, also known as bacterial endocarditis, is caused by bacteria that enter the bloodstream and settle in the endocardium of the heart [3]. It has been established as a pathological infectious process since the nineteenth century [3]. Previously, rheumatic heart disease was the most common aetiology for paediatric IE [4]. However, in recent years, an increase in the survival rate of congenital heart disease (CHD) patients has caused it to become the most common aetiology of paediatric IE [2, 5]. Nevertheless, IE has also been shown to affect children with normal cardiac structures [6]. This is often due to another immunocompromised condition the child may have or a central venous catheter that has been placed in surgery [6]. Infective endocarditis remains challenging in terms of diagnosis and management [7]. Due to the difficulty of performing a randomized control trial for paediatric IE patients, the management of IE has been based on expert opinion [6]. In this review, we aim to provide an overview of paediatric infective endocarditis. We examine the epidemiology, clinical findings, recent updates in diagnostic techniques and more established management approaches to IE in recent years.

Epidemiology and pathophysiology

IE in the paediatric population is a relatively uncommon pathology. However, when it does arise, it has the potential for serious consequences. The crude mortality rate associated with IE has been shown to be as high as up to 25% in cases of native valve endocarditis [8]. Recent estimates predict an incidence between 0.34 and 0.64 cases per 100,000 per year [8]. This epidemiological shift has pointed towards a trend in cases occurring more frequently in those with pre-existing heart disease [9]. Studies have shown that this increase in incidence can be attributed to the increase in survival rate of patients who have had corrective procedures for their CHD [9, 10].

The presence of CHD has been shown to be the biggest identifiable risk factor for IE, resulting in a hundredfold increased risk of IE developing in children (Table 1) [11–18]. Children born with CHDs have an estimated 15–140 times higher risk of developing IE compared to the general population [18]. Mortality and other associated complications are also higher in IE for the CHD population [18]. In the twentieth century, rheumatic heart disease was a major risk factor for IE in the paediatric population [18]. In the 1970s, up to 50% of children with IE had underlying rheumatic disease [1]. In recent times, a shift in aetiology of paediatric IE has been seen with a decreasing incidence of rheumatic disease and an increase in cases without any underlying heart disease [9, 10, 18]. Male gender has also been shown to be at least twice as likely to develop IE in comparison with females [19]. The increased use of indwelling catheters, central lines and other invasive procedures such as surgically implanted shunts, VSD occluders and pacemaker leads has been shown to increase the risk of IE in children (Table 1) [1, 18, 20]. A collection of recent studies found that 12–26% of paediatric IE cases occurred in patients without pre-existing heart disease; however, most of this cohort had been chronically ill, thus likely acquiring their IE from invasive devices such as catheter lines [9].

Being immunocompromised is also a risk factor for the development of paediatric IE. This includes pre-term infants [11] and chronically ill patients that require a long hospital stay (Table 1) [12]. Furthermore, patients undergoing cancer therapy, particularly those requiring bone marrow transplants [13], are at an increased risk of developing IE compared to the general population, both due to immunocompromised and indwelling catheter use during treatment (Table 1) [14]. Associations between patients with DiGeorge syndrome microdeletion 22q11 and IE have been observed, though, due to the wide spectrum of immune status within DiGeorge syndrome, increased study is required to concur an absolute risk (Table 1) [15].

The most common causative organisms that have been reported are *Streptococcus viridans* and *Staphylococcus aureus*, with one study showing 38% and 26% incidence rates respectively across a 30-year period (Table 1) [1, 8–10, 18–21]. In one study, these were found to account for over 60% of the blood culture isolates from paediatric IE patients. Other organisms that have been identified include *Klebsiella* species, *Pseudomonas aeruginosa* and *Enterococcus* species (Table 1). The incidence of *Staphylococcus aureus* as the causative pathogen for IE has increased in recent times, especially in the developed world [9].

The non-specific symptoms that form the presentation of paediatric IE create a diagnostic challenge for clinicians. One of the reasons why paediatric IE is associated with high mortality is due to the failure to effectively recognise the presenting symptoms in children [18]. The spectrum of symptoms varies in different age groups of children. Suspicion of IE can be raised in a previously healthy child who develops fever and anaemia and presents with a heart murmur on auscultation [9, 18, 19].

Right-sided IE implies the involvement of either the tricuspid and/or pulmonary valves (Table 1). Children with CHD and those with indwelling catheters have been shown to present more frequently with right-sided IE [9, 19]. CHDs that affect the right side of the heart, especially tetralogy of Fallot (TOF) and pulmonary atresia (PA), can lead to RVOT (right ventricular outflow tract)

Table 1 Risk factors and aetiology of paediatric infective endocarditis in the cardiac valves [1, 11–17]

Risk factors	Aetiology
Congenital heart defects	*Staphylococcus aureus*
Previous corrective or palliative surgery for cyanotic CHD	*Enterococcus* species
IV alimentation	Viridans group streptococci
Longer durations in ICU	
Transcatheter placement of devices Indwelling catheter	*Klebsiella* species
Normally structured heart without identifiable risk factors Prosthetic valves	*Pseudomonas aeruginosa*
Immunocompromised	HACEK organisms
Cancer therapy (specifically bone marrow transplantation)	Fungi (*Candida*)
DiGeorge syndrome	

HACEK, *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella* and *Kingella*

obstructions which can be potentially fatal [9]. Data collected from a study analysing the characteristics of children with IE showed that inpatient mortality approached 50% in children with CHD such as TOF or PA combined with their IE [9, 10]. Premature infants display higher mortality rates compared to older children [9]. This could be hypothesised to be due to the increased number of invasive procedures the premature infants have to endure to prolong their lives. Paediatric IE has been shown to have an increased risk of thromboembolic complications. This may occur in up to 30% of cases [6, 8]. Pulmonary embolism (PE) has been shown to be a serious complication of right-sided IE and may cause sudden death in patients [6, 8]. Whilst rare, pulmonary valve involvement is not unheard of in paediatric IE, especially in patients with pre-existing CHD [6, 8].

Left-sided IE implies the involvement of the mitral and/or aortic valves (Table 1) with a predilection to the mitral valve over the aortic valve [19]. Left-sided IE has been shown to increase the risk of stroke and subsequent death [22]. Aortic valve IE has shown to have a strong link to heart failure [20]. Heart failure due to aortic valve dysfunction is a known indication for cardiac surgery [20]. Those patients with concurrent IE and HF demonstrate a high risk of mortality [20].

The use of prosthetic valves in cardiac surgery has also been shown to increase the risk of IE development. This is particularly true in children who are aged less than 3 years or those who have had cardiac surgery early in life [18]. The risk of IE when prosthetic valves are used is high in both the immediate postoperative and later periods [1]. A study found that more than a quarter of patients who developed native valve IE had previously undergone surgery to repair the valve [20]. Patients with prosthetic valves that had their infections caused by *Staphylococcus aureus* had poor survival rates indicating an increased severity of illness in this population [1, 9]. The formation of abscesses is also found to be very common in prosthetic valve IE [20].

Diagnostic approaches

Clinical diagnosis

The diagnosis of IE in children is reliant on a holistic strategy for early identification of complications and organisms. The Duke criteria and its later modifications form the basis of IE diagnosis [23, 24]. Two major criteria (positive blood cultures and a positive echocardiogram) and six minor criteria (fever, predisposition, immunological or vascular phenomenon, suggestive echocardiogram and suggestive microbiological findings) allow for stratification into definite, possible and rejected categories [24]. In children, the modified Duke criteria demonstrate a significantly higher accuracy and sensitivity of diagnosis compared to other criteria including the Beth Israel and the Duke criteria [23–25]. Clinical presentations of IE differ between children of different ages, with signs and symptoms seen in adult presentations (such as Janeway lesions and Osler's nodes) being uncommon [16]. It is important to consider IE in children presenting with an antibiotic-resistant fever of unexplained origin, a new cardiac murmur and risk factors such as CHD [16].

Blood cultures

Positive blood cultures remain the most important microbiological test in the diagnosis of IE and its treatment [26]. Aseptic culture techniques are required to avoid cross-contamination of samples [27]. Guidelines recommend 3 cultures are acquired from different venepuncture sites ≥ 1 h apart [28]. This supports rapid diagnosis of acute IE to avoid delays in commencing therapy but is difficult in practice [29]. Culturing requires at least one aerobic and one anaerobic sample collection, with smaller blood samples taken in children compared to adults [1, 30]. Growth of bacteria then requires pathogen identification. Over the past decade, developments in matrix-assisted laser desorption ionisation time-of-flight

mass spectrometry (MALDI-TOF) offered shorter bacterial identification times by up to 1 day [31]. This has since been improved with the potential of bacteraemia microorganism identification within 1 h [32, 33], allowing for significant improvement in the tailoring of initial antibiotic administration. Developments of microbiological practice have additionally led to an increased sensitivity which reduces the incidence of blood culture–negative endocarditis (BCNE) [34]. A 5-day incubation period for collected cultures has been shown to be sufficient to grow the most common causative organisms (such as *Staphylococcus aureus* and viridans streptococci groups), as well as other causative organisms including fungi (*Candida*) and difficult to grow bacteria (i.e. HACEK organisms; *Haemophilus*, *Aggregatibacter*, *Cardiobacterium*, *Eikenella* and *Kingella* organisms) [16, 17]. These less-common organisms previously required longer incubation periods [30]. If these pathogens are suspected, laboratory staff should be made aware to help improve chances of identification [1].

BCNE, often due to antimicrobials in the bloodstream during blood collection, represents up to 40% of all IE cases [35]. In patients undergoing antibiotic therapy, cessation for a sample collection is recommended, although this must be discussed in advance with a senior clinician [1, 30]. Other common etiologies of BCNE include *C. burnetti* and *Bartonella* species for which serology testing and IgG titres prove more useful in diagnosis as well as real-time polymerase chain reaction assays which target various causative organisms such as *Mycoplasma* [28, 30, 35–37].

Imaging techniques

The use of echocardiography is crucial in the diagnosis of IE. It provides an insight through identification of valvular vegetations, chamber dysfunction and perivalvular disease. Transthoracic echocardiogram (TTE) is the least invasive and yields the most efficient visualisation of vegetations, lending itself to being the first-line investigative imaging technique [28]. TTE harbours a relatively low sensitivity and thus cannot rule out IE, so transoesophageal echocardiogram (TOE) is recommended for picking up missed vegetations and local complications [28, 38]. In children, the diagnostic yield of TOE is seen as minimal in cases of incomplete Duke's criteria and should only be used in classifications of possible IE in native hearts [39]. 2D TOE shows a higher sensitivity when directly compared with 3D TOE, though 2D TOE is less able to distinguish between vegetation morphologies [40, 41]. Distinguishing between vegetations would allow for further quantification of IE risk and future management options [41, 42]. In addition, utilisation of 3D TOE in conjunction with 2D TOE has been shown to provide an additional value to diagnostic techniques in up to 33% of cases [43]. 3D TOE is of particular importance in highly specialised centres, primarily when increased visualisation accuracy is required such as in surgical planning [44].

Computed tomography (CT) improves the yield of IE diagnosis significantly [45]. CT functions at a higher specificity compared to TOE, particularly in prosthetic valve and device IE [46]. The importance of CT lies in the identification of extra-cardiac features of disease such as embolic infection and can lend itself to increased specific management whilst being minimally invasive [47].

18-F-Fluorodeoxyglucose-positron emission tomography/CT (FDG-PET/CT) has shown particular promise in investigating prosthetic valve IE. FDG-PET/CT identifies higher metabolic activity within the body that echocardiography is liable to misinterpret as device artefact instead of disease [48]. FDG-PET/CT improves the diagnostic specificity of the modified Duke criteria in prosthetic valves through distinguishing definite IEs from possible IEs [49]. FDG-PET/CT can also be utilised to identify extra-cardiac complications such as septic emboli [48]. However, identification of intra-cardiac complications through this modality has shown to be unsatisfactory, especially in patients with suspected native valve IE [50]. The use of this modality is also limited by a large dependency on adequate patient preparation prior to scan [51].

Biomarkers

Although biomarkers are not sought when diagnosing IE, they are valuable in the prognostication process. Recent literature supports the use of interleukin-15, C-C motif chemokine ligand (CCF4) and C-reactive protein (CRP) to improve the accuracy of risk prediction [52]. Whilst CRP is a non-specific marker of infection, its significance in predicting morbidity and mortality in IE appears regularly in literature [53, 54]. CRP can be used as an independent predictor of infection through positive associations with FDG-PET/CT findings (outlined as identification of causes of fever of unexplained origin in children) [55]. Additionally, baseline CRP (collected within the first 3 days of admission) has shown to be a strong predictor of major short-term complications in endocarditis, particularly if a reading over > 40mg/L is found [53].

Management

When a definitive diagnosis of IE has been made, the decision to carry out medical management or surgical intervention is decided following a multidisciplinary team discussion [28]. Regardless of the management option selected, the shared objective of microbial eradication is maintained in order to minimise complications such as heart failure, abscess formation and systemic embolisation [1, 28].

Medical intervention

Once the diagnosis has been established, appropriate therapy should be commenced as early as possible using local antibiotic guidance on early empirical therapy and targeted treatment based on culture and sensitivities [1]. A prolonged course of intravenous empirical antibiotics for a minimum of 4 weeks (often 6–8 weeks) is recommended to cover the period of vegetation formation [1]. Bactericidal agents are favoured over bacteriostatic drugs as previous data has reported relapses and treatment failure with the therapeutic use of bacteriostatic antibiotics alone [1]. A full course of antimicrobial treatment should commence following positive blood cultures and the selection of antibiotics is based on the antibiogram (susceptibility of the bacterial isolate) [1]. If patients have negative blood cultures, antibiotics can be withheld for ≥ 48 h until further blood cultures are obtained under the circumstances that these patients are not severely ill and are clinically stable with no signs of altered mental status or haemodynamic/respiratory compromise [1]. The antibiotic treatment for paediatric IE according to the European Society of Cardiology guidelines is outlined in Table 2 [28].

Surgical intervention (repair vs replacement)

Surgical intervention can be lifesaving in children at a higher risk of developing life-threatening complications where a cure by antimicrobial therapy alone is deemed to be insufficient [1]. Irrespective of whether surgical management is necessary, patients are commenced on IV antibiotics as per guidelines [1]. Some of the risk factors requiring surgery include prosthetic cardiac valves, prolonged clinical symptoms lasting more than 3 months, previous IE, *Staphylococcus aureus* IE, fungal IE, left-sided IE, presence of systemic-to-pulmonary shunts, cyanotic congenital heart disease and persistent bacteraemia despite antimicrobial treatments [1]. Heart failure is the commonest and most severe complication of IE. Hence, the manifestation of HF ± cardiogenic shock indicates the need for early surgical intervention in both native and prosthetic valve IE, unless the patient has an existing severe comorbidity [28]. Other important indications for surgical therapy include progressive valvular dysfunction and threatened or proven systemic embolization of vegetations [1, 56, 57].

The decision to perform a valve repair versus valve replacement depends on the degree of valvular or great vessel root damage [1]. The principal objectives of surgical intervention include the total excision of infected tissues and reconstructing cardiac morphology by valvular repair or replacement [6]. If the infection is confined to the valve, either technique is appropriate though valvular replacement should be avoided where possible [28]. Preservation of the native tissue by valve debridement/repair is desirable in younger children as it is associated with freedom from re-operation, improved survival and late functional status outcomes [58, 59]. Valve repair is the favourable option in mitral/tricuspid valve endocarditis without extensive damage and is also carried out in single valve cusp/leaflet or leaflet perforations and ruptured chordae. The presence of an abscess or extensive damage of a single leaflet does not exclude valve repair. Instead, intraoperative valvular assessment following debridement can be used to evaluate whether the residual valve tissue is sufficient for repair alone [28]. Preoperative features associated with valvular replacement consist of increased leaflet thickening and incidence of embolisation [58]. Valve replacement is also indicated in the presence of locally uncontrolled infection and difficult cases which may require intraoperative repair of associated congenital defects to avoid paravalvular leaks and secure the valve [28]. Whilst many patients may need additional surgical procedures in the future, the long-term survival is satisfactory [28].

Children with congenital heart disease often require a pulmonary valve implant [60]. Transcatheter pulmonary valve (TPV) replacement is increasingly being used in right ventricular outflow tract conduit dysfunction. Whilst this therapeutic option has good functional results, device-related IE is an important complication due to an increasing occurrence [61]. Prosthetic valve endocarditis is a life-threatening condition which can be fatal [60]. Multiple studies have evaluated surgically implanted (Contegra conduit) and transcatheter (Melody valve stent) options for right ventricular outflow tract reconstruction. All of these studies have reported an increased incidence of IE in bovine jugular vein (BJV) pulmonary conduits (Contegra and Melody) compared with cryopreserved homografts [62–67]. A more recent study reported Melody valves having a higher frequency of infection in bovine pulmonary conduits [66]. Though there is no comprehensive explanation as to why BJV valves are associated with higher frequency of IE, Sharma et al. suggested that the substrate for infectivity is associated with the type of tissue instead of implantation method [67]. Whilst the exact causative mechanism remains unknown, Gierlinger et al. have reported safe and effective surgical treatment of percutaneous pulmonary valve prosthesis IE if patients are referred early enough [60].

Current guidelines (American and European guidelines)

In 2015, the AHA and ESC updated their guidelines for the diagnosis and treatment of paediatric IE [6, 68]. ESC highlighted the importance of an endocarditis team comprising a cardiologist, cardiac surgeon, microbiologist and infectious disease specialist with the addition of new imaging modalities to approve the safety of early surgical intervention [68]. The ESC indications for surgical intervention are similar to the guidelines published by the AHA which include heart failure, preventing embolic phenomena and uncontrolled

Table 2 ESC antibiotic treatment for paediatric infective endocarditis [28]

Strains	Antibiotic	Dosage	Duration (weeks)	Patients
Streptococci and *Streptococcus bovis*	IV Penicillin G or IV Amoxicillin or IV Ceftriaxone	200,000 U/kg/day 300 mg/kg/day 100 mg/kg/day	4 (NVE), 6 (PVE)	Age > 65 Impaired renal or cranial nerve VIII functions
	IV Penicillin G or IV Amoxicillin or IV Ceftriaxone + IV Gentamicin	200,000 U/kg/day 300 mg/kg/day 100 mg/kg/day 3 mg/kg/day	2	Non complicated NVE and normal renal function
	IV Vancomycin	40/mg/mg/day	4	Beta lactam allergic patients
Streptococci (relatively resistant to penicillin)	IV Penicillin G or IV Amoxicillin or IV Ceftriaxone + IV Gentamicin	200,000 U/kg/day 300 mg/kg/day 100 mg/kg/day 3 mg/kg/day	4 (NVE), 6 (PVE) 2	
	IV Vancomycin + IV Gentamycin	40/mg/mg/day 3 mg/kg/day	4 (NVE), 6 (PVE) 2	Beta lactam allergic patients
Methicillin-susceptible *Staphylococci* (NVE)	IV Flucloxacillin or IV Oxacillin *Alternative* Cotrimoxazole + IV Clindamycin	200–300 mg/kg/day Sulfamethoxazole 60 mg/kg/day and IV Trimethoprim 12 mg/kg/day 40 mg/kg/day	4–6 1 IV + 5 oral 1	
Methicillin-susceptible *Staphylococci* (PVE)	IV Flucloxacillin or Oraxillin + IV Rifampin + IV Gentamicin	200–300 mg/kg/day 20 g/kg/day 3 mg/kg/day	≥ 6 ≥ 6 2	Experts have suggested starting Rifampin 3–5 days after Gentamicin Single daily dose to reduce renal toxicity
Methicillin-resistant *Staphylococci* (NVE)	IV Vancomycin or IV Daptomycin or Cotrimoxazole + IV Clindamycin	40/mg/mg/day 10 mg/kg/day Sulfamethoxazole 60 mg/kg/day and IV Trimethoprim 12 mg/kg/day 40 mg/kg/day	4–6 4–6 1 IV + 5 oral 1	
Methicillin-resistant *Staphylococci* (PVE) and penicillin-allergic patients	IV Vancomycin + IV Rifampin + IV Gentamicin	40/mg/mg/day 20 g/kg/day 3 mg/kg/day	≥ 6 ≥ 6 2	
Enterococcus	IV Amoxicillin + IV Gentamicin	300 mg/kg/day 3 mg/kg/day	4–6 2–6	6-week therapy in PVE and symptoms persisting > 3 months
	IV Ampicillin + IV Ceftriaxone	300 mg/kg/day 100 mg/kg/12h	6 6	Effective against HLAR *E. faecalis* endocarditis Not effective against *E. faecium*
	IV Vancomycin + IV Gentamycin	40 mg/kg/day 3 mg/kg/day	6 6	Penicillin allergic
HACEK gram-negative bacilli	IV ceftriaxone or IV cefotaxime or IV Gentamicin (cefotaxime alternative) IV Ampicillin IV Amikacin (Ampicillin alternative)	100mg/kg/12h Or 80mg/kg/day 200mg/kg/6h 3–6mg/kg/8h 200–300mg/kg/4–6h 15mg/kg/8–12h	4 (NVE), 6 (PVE) 4–6	HACEK-group bacilli producing beta-lactamases HACEK group bacilli not producing beta-lactamases
Fungal	IV Amphotericin B (with or without flucytosine) + surgical resection or oral flucytosine	1mg/kg/3–4h 150mg/kg/6h		

infection [1, 28]. These keep in line with the 2016 American Association for Thoracic Surgery guidelines [6]. Even though a consensus has been obtained for the majority of medical management with antibiotics, there are still debates about the empirical treatment and optimal management of staphylococcal IE. The AHA guidelines suggest the addition of

gentamicin in the first 3–5 days of treatment to oxacillin in methicillin-sensitive strains on NVE, whilst the ESC guidelines do not recommend the addition of gentamicin due to concerns of toxicity and insufficient evidence of efficacy [68].

Prophylaxis

The risk factors for developing IE include dental procedures, CHD, history of previous IE, repaired CHD with residual defects and any CHD repaired within the last 6 months involving insertion of prosthetic material [69]. Although prophylaxis has been recommended in the past, NICE guidelines now call for cessation of any antibiotic prophylaxis for IE prevention [70]. Additionally, the AHA also relaxed antibiotic prophylaxis use in 2007 [69, 70]. Despite the reduction of prophylaxis use in the recent decade, large increases in IE incidence have not been found [71]. This may, however, be due to continued antibiotic prophylaxis prescriptions despite recommendations, with literature concluding only 44% of clinicians exclusively follow these guidelines [72]. Yet reports and reviews have concluded an overuse of antibiotic medication prior to 2007 [73]. These findings bring into question whether cessation of antibiotic prophylaxis use is more desirable for paediatric IE in non-high-risk groups [69, 73]. However, the importance of good dental hygiene and prompt treatment in suspected infections remains important in IE prevention [70, 74].

Length of treatment and monitoring

A prolonged duration of intravenous antibiotics—for a minimum of 4 weeks and often for between 6 and 8 weeks—is indicated to treat bacterial endocarditis. The duration may be further prolonged (for at least 6 weeks) in recurrent endocarditis, prosthetic valve endocarditis, fungal endocarditis and endocarditis caused by uncommon species [1, 6]. A prolonged antibiotic duration is indicated as the infection is established in a biofilm matrix which occurs by the deposition of fibrin and platelets on injured vascular endothelium [57]. The organisms are contained and exist in high concentrations within the fibrin-platelet matrix which isolates the bacteria from antibiotics or neutrophils in the bloodstream, making them tolerant to bactericidal killing [1, 57].

It is important to monitor patients over the course of their treatment for complications of the infection, adherence to drug therapy and presence of drug toxicity [1]. In order to monitor the adequacy of drug treatment, daily blood cultures need to be repeated until they come back sterile as this marks the elimination of bacteraemia [1]. In order to further ensure cure, additional blood cultures can be performed within 8 weeks of completing antibiotic treatment; however, this risks the isolation of a contaminant [1, 2].

Timing of surgery

The three main indications for early surgical intervention are heart failure, prevention of embolic events and uncontrolled infection [28]. Early surgical intervention is important in order to prevent progression to acute heart failure, systemic thromboembolic phenomena and irreversible structural damage [28]. The ESC guidelines suggest that, depending on the severity of the case, a decision to carry out emergency surgery (within 24 h) or urgent surgery (within 7 days) needs to be made regardless of antibiotic treatment [68]. Cases requiring emergency surgery include persistent pulmonary oedema and cardiogenic shock [28]. Urgent surgeries are carried out in cases of severe mitral and aortic valve insufficiency alongside large vegetations, even in the absence of heart failure [56]. On the other hand, when heart failure is less severe, such cases can undergo an elective surgical procedure following 1–2 weeks of medical management with antibiotics. These patients require close clinical and echocardiographic monitoring prior to surgery. A 15-year review of paediatric IE carried out by Shamszad et al. reported that most patients underwent surgical intervention within 7 days of diagnosis, with half of the cohort undergoing surgery within 3 days due to *Staphylococcus aureus* infection or ventricular dysfunction [21]. They reported successful early surgery with low rates of recurrence/mortality and high rates of native valve repair [21]. Various studies have demonstrated favourable outcomes following early surgical intervention in children as it is associated with low morbidity and mortality [28, 56, 75].

Long-term outcomes

There is limited data regarding the long-term outcomes of paediatric IE patients [20]. However, a study evaluating the outcomes of surgical management in children with endocarditis over a 30-year period between 1987 and 2017 found operative mortality to be 5.8% and long-term survival at 5 and 25 years to be 91.5% and 79.1% respectively. Freedom from recurrent endocarditis was reported to be 94.7%, eluding to a good long-term survival and low risk of IE recurrence [20]. This reflects on a good overall prognosis for surgical management of endocarditis.

Similarly, a 15-year retrospective review found that, compared to those undergoing non-surgical management, patients who had their endocarditis surgically managed had a lower rate of repeat valve replacements. It was also found that early surgery on children can be performed with low postoperative mortality and acceptable outcomes [21]. This highlights surgery provides a better definitive cure in comparison to medical management using antibiotics. However, in more complicated paediatric IE cases, antibiotic therapy as well as surgical intervention may be also be required.

Although there have not been many studies comparing the outcomes of paediatric patients undergoing medical versus surgical therapy, a long-term follow-up by the Cleveland Clinic found there to be no overall difference in long-term prognosis based on the mode of therapy (medical vs medical and surgical) in the group of paediatric patients treated [76]. Regardless of whether surgical management is used or not, antibiotic therapy is critical in reducing the risk of new embolic events with a risk of only 9–21% after starting therapy compared to 20–40% in those not treated with antibiotics [77]. This demonstrates a conflict of results between the studies mentioned [20, 21, 76].

Outcomes following treatment are dependent on several factors rather than the form of management alone; this includes the severity of the episode of endocarditis, the prior long-term health and medical history of the patient and most importantly the causative organism. This was reflected in a Tunisian study which found mortality at a 6-month follow-up to be significantly associated with the presence of heart failure, acute renal failure and neurological complications on admission [78]. This study also found coagulase-negative staphylococci and increased duration of preoperative antibiotic therapy to be significant risk factors associated with an overall worse outcome.

Quality of life

Quality of life has a positive outlook in the majority of paediatric IE patients; however, there are variations depending on the particular individuals' prior health/well-being and severity of the infective episode, which subsequently dictates the invasiveness of their required management. Patients after valve replacement surgery may require long-term anticoagulation with warfarin to prevent any thromboembolic events and would need to be regularly followed up and monitored to maintain therapeutic levels [79]. This is especially necessary in patients who have undergone a mitral valve replacement, after which the chronic anticoagulation required in these patients can be poorly tolerated and difficult to manage [80].

Since surgical management is required in patients with more severe and complicated cases of IE, the outcomes are consequently poorer compared to cases managed medically (i.e. with antibiotics) which are more likely to be without complications. Khoo B et al. conducted a 30-year follow-up which showed that heart failure was the most common indication for surgery in the active group of patients surgically managed from their sample of patients. Risk factors found to be independently associated with reoperation were prior cardiac surgery and perivalvular abscess [20]. Freedom of recurrence of IE was 95% at 25 years of follow-up as only 2 patients required reoperation for recurrent endocarditis [79]. It could be concluded that surgery was highly effective in curing IE in children and has a very good overall prognosis for the patient's well-being [79].

One of the more frequent complications of IE includes heart failure which can occur acutely or insidiously. The management of progressive valvular damage and the resulting complication of heart failure with medical therapy alone is often unsuccessful, leading to issues postoperatively and possible repeat hospital admissions leading to poorer health and thus a detrimental effect on the patient's quality of life [2].

Limitations

Due to the low prevalence of IE in children, the literature surrounding the topic is limited with the majority being compiled of either case reports with commentaries or retrospective cohort studies with small-moderate sample sizes [8–10, 18, 20–22]. This leads to a number of potential issues including the risk of potential biases such as selection and reporting bias [81]. The lack of large samples also risks negative endpoints being observed due to a lack of statistical power and makes it difficult to exclude type II errors for this reason. The retrospective nature of a number of the studies can also lead to information bias due to misdiagnosis, improper coding and poor registration quality as variables were not being considered in advance [81]. Although it would be ideal for large-scale interventional studies to be carried out in this population, it is implausible to find randomised controlled trials for the treatment of IE in children.

Antimicrobial therapy recommendations for IE in paediatrics generally come from review of experience, as opposed to experimental study; therefore, it is difficult to compare therapies with each other. The recommendations are often based on adult guidelines, expert opinion and qualitative interpretation of paediatric reviews [82]. In addition to this, the recommendation of surgical intervention for IE in children is also derived from their adult equivalents with expert opinion [1].

Future studies with larger numbers of patients and a greater focus on the paediatric population are required in order to establish clearer guidelines for the investigation, diagnosis and treatment (both antimicrobial and surgical) management of IE in children [1].

Conclusion

Modern-day improvements in paediatric cardiac surgery have led to an increased number of children and young adults living with repaired or palliated congenital heart disease who are at increased risk of IE, in addition to children who develop IE with structurally normal hearts. There is mixed opinion on the necessity of antibiotic prophylaxis against IE in high-risk patients undergoing dental procedures and further work is

necessary in order to reach a consensus. Overall, IE in the paediatric population has a good long-term survival and low risk of recurrence following surgical management. However, early detection, treatment and prevention of complications in this population needs deeper understanding and strategy.

Abbreviations *AHA,* The American Heart Association; *BCNE,* Blood culture–negative endocarditis; *CCF4,* C-C motif chemokine ligand; *CHD,* Congenital heart disease; *CRP,* C-reactive protein; *CT,* Computed tomography; *ESC,* European Society of Cardiology; *FDG-PET/CT,* F-Fluorodeoxyglucose-positron emission tomography; *HF,* Heart failure; *IE,* Infective endocarditis; *PA,* Pulmonary atresia; *PE,* Pulmonary embolism; *RVOT,* Right ventricular outflow tract; *TOE,* Transoesophageal echocardiogram; *TOF,* Tetralogy of Fallot; *TTE,* Transthoracic echocardiogram; *VSD,* Ventricular septal defect

Availability of data and material N/A

Code availability N/A

Authors' contributions L.E has contributed to writing the manuscript, editing and approving the final manuscript; A.K. has contributed to writing the manuscript, editing and approving the final manuscript; G.M. has contributed to writing the manuscript, editing and approving the final manuscript; A.C. has contributed to writing the manuscript, editing and approving the final manuscript; S.S. has contributed to writing the manuscript, editing and approving the final manuscript; A.S. has contributed to writing the manuscript, editing and approving the final manuscript; A.T. contributed to reviewing the draft manuscript, critically appraising, amending and approving the final manuscript; A.H come up with the topic, design of the study, critically reviewed the manuscript and edited it and wrote the manuscript as well as approved the final manuscript.

Declarations

Ethics approval N/A

Consent to participate N/A

Consent for publication N/A

Conflict of interest The authors declare no competing interests.

References

1. Baltimore RS, Gewitz M, Baddour LM, Beerman LB, Jackson MA, Lockhart PB, Pahl E, Schutze GE, Shulman ST, Willoughby R Jr, American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee of the Council on Cardiovascular Disease in the Young and the Council on Cardiovascular and Stroke Nursing (2015) Infective endocarditis in childhood: 2015 update: a scientific statement from the American Heart Association. Circulation. 132(15):1487–1515
2. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, Wilson W, Bolger AF, Bayer A, Levison ME, Pallasch TJ, Gage TW, Taubert KA, From the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease of the American Heart Association Council on Cardiovascular Disease in the Young (2002) Unique features of infective endocarditis in childhood. Circulation. 105(17):2115–2126
3. Holland TL, Baddour LM, Bayer AS, Hoen B, Miro JM, Fowler VG Jr (2016) Infective endocarditis. Nat Rev Dis Primers 2:16059
4. Ahmadi A, Daryushi H (2014) Infective endocarditis in children: a 5 year experience from Al-Zahra Hospital, Isfahan, Iran. Adv Biomed Res 3:228
5. Tseng WC, Chiu SN, Shao PL, Wang JK, Chen CA, Lin MT, Lu CW, Wu MH (2014) Changing spectrum of infective endocarditis in children: a 30 years experiences from a tertiary care center in Taiwan. Pediatr Infect Dis J. 33(5):467–471
6. Nasser BA, Al Qwaee A, Almesned AR, Akhfash A, Mohamad T, Chaikhouni F et al (2019) Infective endocarditis in children with normal heart: indication for surgical intervention. J Saudi Heart Assoc. 31(2):51–56
7. Kelchtermans J, Grossar L, Eyskens B, Cools B, Roggen M, Boshoff D, Louw J, Frerich S, Veloso TR, Claes J, Ditkowski B, Rega F, Meyns B, Gewillig M, Heying R (2019) Clinical characteristics of infective endocarditis in children. Pediatr Infect Dis J. 38(5):453–458
8. Thom K, Hanslik A, Russell JL, Williams S, Sivaprakasam P, Allen U, Male C, Brandão LR (2018) Incidence of infective endocarditis and its thromboembolic complications in a pediatric population over 30years. Int J Cardiol. 252:74–79
9. Lin YT, Hsieh KS, Chen YS, Huang IF, Cheng MF (2013) Infective endocarditis in children without underlying heart disease. J Microbiol Immunol Infect. 46(2):121–128
10. Day MD, Gauvreau K, Shulman S, Newburger JW (2009) Characteristics of children hospitalized with infective endocarditis. Circulation. 119(6):865–870
11. Day MD, Gauvreau K, Shulman S, Newburger JW (2009) Characteristics of children hospitalised with infective endocarditis. Circulation. 119(6):865–879
12. Rosenthal LB, Feja KN, Levasseur SM, Alba LR, Gersony W, Seiman L (2010) The changing epidemiology of paediatric endocarditis at a children's hospital over seven decades. Paediatr Cardiol 31(6):813–820
13. Kuruvilla K, Forrest DL, Lavoie JC, Nantel SH, Shepherd JD, Song KW, Sutherland HJ, Toze CL, Hogge DE, Nevill TJ (2004) Characteristics and outcome of patients developing endocarditis following hematopoietic stem cell transplantation. Bone Marrow Transplantation. 34(11):969–973
14. Rech A, Loss JF, Machado A, Brunetto AL (2004) Infective endocarditis (IE) in children receiving treatment for cancer. Pediatric Blood and Cancer. 43(2):159–163
15. Sadeghi S, Wadia S, Lluri G, Tarabay J, Fernando A, Salem M, Sinha S, Levi DS, Aboulhosn J (2019) Risk factors for infective endocarditis following transcatheter pulmonary valve replacements in patients with congenital heart disease. Catheterization and Cardiovascular Interventions. 94(4):625–635
16. Gupta S, Sakhuja A, McGrath E, Asmar B (2017) Trends, microbiology, and outcomes of infective endocarditis in children during 2000-2010 in the United States. Congenit Heart Dis. 12(2):196–201
17. Chambers ST, Murdoch D, Morris A, Holland D, Pappas P, Almela M, Fernández-Hidalgo N, Almirante B, Bouza E, Forno D, Rio A, Hannan MM, Harkness J, Kanafani ZA, Lalani T, Lang S, Raymond N, Read K, Vinogradova T, Woods CW, Wray D, Corey GR, Chu VH, International Collaboration on Endocarditis Prospective Cohort Study (ICE-PCS) Investigators (2013) HACEK infective endocarditis: characteristics and outcomes from a large, multi-national cohort. PLoS One. 8(5):e63181
18. Jortveit J, Klcovansky J, Eskedal L, Birkeland S, Døhlen G, Holmstrøm H (2018) Endocarditis in children and adolescents with congenital heart defects: a Norwegian nationwide register-based cohort study. Arch Dis Child. 103(7):670–674

19. Knirsch W, Nadal D (2011) Infective endocarditis in congenital heart disease. Eur J Pediatr. 170(9):1111–1127
20. Khoo B, Buratto E, Fricke TA, Gelbart B, Brizard CP, Brink J, d'Udekem Y, Konstantinov IE (2019) Outcomes of surgery for infective endocarditis in children: a 30-year experience. J Thorac Cardiovasc Surg. 158(5):1399–1409
21. Shamszad P, Khan MS, Rossano JW, Fraser CD Jr (2013) Early surgical therapy of infective endocarditis in children: a 15-year experience. J Thorac Cardiovasc Surg. 146(3):506–511
22. Cao GF, Bi Q (2019) Pediatric infective endocarditis and stroke: a 13-year single-center review. Pediatr Neurol. 90:56–60
23. Durack DT, Lukes AS, Bright DK (1994) New criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Duke Endocarditis Service. Am J Med. 96(3):200–209
24. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG Jr, Ryan T et al (2000) Proposed modifications to the Duke criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 30(4):633–638
25. Stockheim JA, Chadwick EG, Kessler S, Amer M, Abdel-Haq N, Dajani AS, Shulman ST (1998) Are the Duke criteria superior to the Beth Israel criteria for the diagnosis of infective endocarditis in children? Clin Infect Dis. 27(6):1451–1456
26. Chambers HF, Bayer AS (2020) Native-valve infective endocarditis. N Engl J Med. 383(6):567–576
27. Dawson S (2014) Blood culture contaminants. J Hosp Infect. 87(1): 1–10
28. Habib G, Lancellotti P, Antunes MJ, Bongiorni MG, Casalta JP, Del Zotti F et al (2015) 2015 ESC Guidelines for the management of infective endocarditis: the Task Force for the Management of Infective Endocarditis of the European Society of Cardiology (ESC). Endorsed by: European Association for Cardio-Thoracic Surgery (EACTS), the European Association of Nuclear Medicine (EANM). Eur Heart J. 36(44):3075–3128
29. Gould FK, Denning DW, Elliott TS, Foweraker J, Perry JD, Prendergast BD et al (2012) Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the Working Party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother. 67(2):269–289
30. Liesman RM, Pritt BS, Maleszewski JJ, Patel R (2017) Laboratory diagnosis of infective endocarditis. J Clin Microbiol. 55(9):2599–2608
31. La Scola B, Raoult D (2009) Direct identification of bacteria in positive blood culture bottles by matrix-assisted laser desorption ionisation time-of-flight mass spectrometry. PLoS One. 4(11): e8041
32. Azrad M, Keness Y, Nitzan O, Pastukh N, Tkhawkho L, Freidus V, Peretz A (2019) Cheap and rapid in-house method for direct identification of positive blood cultures by MALDI-TOF MS technology. BMC Infect Dis. 19(1):72
33. Wang Y, Jin Y, Bai Y, Song Z, Chu W, Zhao M, Hao Y, Lu Z (2020) Rapid method for direct identification of positive blood cultures by MALDI-TOF MS. Exp Ther Med. 20(6):235
34. Elder RW, Baltimore RS (2015) The changing epidemiology of pediatric endocarditis. Infect Dis Clin North Am. 29(3):513–524
35. Lamas CC, Fournier PE, Zappa M, Brandão TJ, Januário-da-Silva CA, Correia MG et al (2016) Diagnosis of blood culture-negative endocarditis and clinical comparison between blood culture-negative and blood culture-positive cases. Infection. 44(4):459–466
36. Houpikian P, Raoult D (2005) Blood culture-negative endocarditis in a reference center: etiologic diagnosis of 348 cases. Medicine (Baltimore). 84(3):162–173
37. Fournier PE, Gouriet F, Casalta JP, Lepidi H, Chaudet H, Thuny F, Collart F, Habib G, Raoult D (2017) Blood culture-negative endocarditis: improving the diagnostic yield using new diagnostic tools. Medicine (Baltimore). 96(47):e8392
38. Bai AD, Steinberg M, Showler A, Burry L, Bhatia RS, Tomlinson GA et al (2017) Diagnostic accuracy of transthoracic echocardiography for infective endocarditis findings using transesophageal echocardiography as the reference standard: a meta-analysis. J Am Soc Echocardiogr 30(7):639-46.e8
39. Kelly P, Hua N, Madriago EJ, Holmes KW, Shaughnessy R, Ronai C (2020) The utility of echocardiography in pediatric patients with structurally normal hearts and suspected endocarditis. Pediatr Cardiol. 41(1):62–68
40. García-Orta R, Moreno E, Vidal M, Ruiz-López F, Oyonarte JM, Lara J, Moreno T, García-Fernándezd MA, Azpitarte J (2007) Three-dimensional versus two-dimensional transesophageal echocardiography in mitral valve repair. J Am Soc Echocardiogr. 20(1):4–12
41. Pfister R, Betton Y, Freyhaus HT, Jung N, Baldus S, Michels G (2016) Three-dimensional compared to two-dimensional transesophageal echocardiography for diagnosis of infective endocarditis. Infection. 44(6):725–731
42. Berdejo J, Shibayama K, Harada K, Tanaka J, Mihara H, Gurudevan SV, Siegel RJ, Shiota T (2014) Evaluation of vegetation size and its relationship with embolism in infective endocarditis: a real-time 3-dimensional transesophageal echocardiography study. Circ Cardiovasc Imaging. 7(1):149–154
43. Tanis W, Teske AJ, van Herwerden LA, Chamuleau S, Meijboom F, Budde RP et al (2015) The additional value of three-dimensional transesophageal echocardiography in complex aortic prosthetic heart valve endocarditis. Echocardiography. 32(1):114–125
44. Galzerano D, Kinsara AJ, Di Michele S, Vriz O, Fadel BM, Musci RL et al (2020) Three dimensional transesophageal echocardiography: a missing link in infective endocarditis imaging? Int J Cardiovasc Imaging. 36(3):403–413
45. Jain V, Wang TKM, Bansal A, Farwati M, Gad M, Montane B, Kaur S, Bolen MA, Grimm R, Griffin B, Xu B (2020) Diagnostic performance of cardiac computed tomography versus transesophageal echocardiography in infective endocarditis: a contemporary comparative meta-analysis. J Cardiovasc Comput Tomogr.
46. Feuchtner GM, Stolzmann P, Dichtl W, Schertler T, Bonatti J, Scheffel H, Mueller S, Plass A, Mueller L, Bartel T, Wolf F, Alkadhi H (2009) Multislice computed tomography in infective endocarditis: comparison with transesophageal echocardiography and intraoperative findings. J Am Coll Cardiol. 53(5):436–444
47. Erba PA, Pizzi MN, Roque A, Salaun E, Lancellotti P, Tornos P, Habib G (2019) Multimodality imaging in infective endocarditis: an imaging team within the endocarditis team. Circulation. 140(21): 1753–1765
48. Orvin K, Goldberg E, Bernstine H, Groshar D, Sagie A, Kornowski R, Bishara J (2015) The role of FDG-PET/CT imaging in early detection of extra-cardiac complications of infective endocarditis. Clin Microbiol Infect. 21(1):69–76
49. Saby L, Laas O, Habib G, Cammilleri S, Mancini J, Tessonnier L, Casalta JP, Gouriet F, Riberi A, Avierinos JF, Collart F, Mundler O, Raoult D, Thuny F (2013) Positron emission tomography/computed tomography for diagnosis of prosthetic valve endocarditis: increased valvular 18F-fluorodeoxyglucose uptake as a novel major criterion. J Am Coll Cardiol. 61(23):2374–2382
50. Granados U, Fuster D, Pericas JM, Llopis JL, Ninot S, Quintana E, Almela M, Pare C, Tolosana JM, Falces C, Moreno A, Pons F, Lomena F, Miro JM, Hospital Clinic Endocarditis Study Group (2016) Diagnostic accuracy of 18F-FDG PET/CT in infective endocarditis and implantable cardiac electronic device infection: a cross-sectional study. J Nucl Med. 57(11):1726–1732
51. Jiménez-Ballvé A, Pérez-Castejón MJ, Delgado-Bolton RC, Sánchez-Enrique C, Vilacosta I, Vivas D, Olmos C, Ferrer MEF, Carreras-Delgado JL (2016) Assessment of the diagnostic accuracy of (18)F-FDG PET/CT in prosthetic infective endocarditis and cardiac implantable electronic device infection: comparison of different interpretation criteria. Eur J Nucl Med Mol Imaging. 43(13):2401–2412
52. Ris T, Teixeira-Carvalho A, Coelho RMP, Brandao-de-Resende C, Gomes MS, Amaral LR, Pinto PHOM, Santos LJS, Salles JT,

Roos-Hesselink J, Verkaik N, Ferrari TCA, Nunes MCP (2019) Inflammatory biomarkers in infective endocarditis: machine learning to predict mortality. Clin Exp Immunol. 196(3):374–382
53. Mohanan S, Gopalan Nair R, Vellani H, C GS, George B, M NK (2018) Baseline C-reactive protein levels and prognosis in patients with infective endocarditis: a prospective cohort study. Indian Heart J 70(Suppl 3(Suppl 3)):S43-s9
54. Nunes MCP, Guimarães-Júnior MH, Murta Pinto PHO, Coelho RMP, Souza Barros TL, Faleiro Maia NPA et al (2018) Outcomes of infective endocarditis in the current era: early predictors of a poor prognosis. Int J Infect Dis. 68:102–107
55. Pijl JP, Kwee TC, Legger GE, Peters HJH, Armbrust W, Schölvinck EH, Glaudemans AWJM (2020) Role of FDG-PET/CT in children with fever of unknown origin. Eur J Nucl Med Mol Imaging. 47(6):1596–1604
56. Kang DH, Kim YJ, Kim SH, Sun BJ, Kim DH, Yun SC, Song JM, Choo SJ, Chung CH, Song JK, Lee JW, Sohn DW (2012) Early surgery versus conventional treatment for infective endocarditis. N Engl J Med. 366(26):2466–2473
57. Citak M, Rees A, Mavroudis C (1992) Surgical management of infective endocarditis in children. Ann Thorac Surg. 54(4):755–760
58. Hickey EJ, Jung G, Manlhiot C, Sakopoulos AG, Caldarone CA, Coles JG, van Arsdell GS, McCrindle BW (2009) Infective endocarditis in children: native valve preservation is frequently possible despite advanced clinical disease. Eur J Cardiothorac Surg. 35(1):130–135
59. Alexiou C, Langley SM, Monro JL (1999) Surgery for infective valve endocarditis in children. Eur J Cardiothorac Surg. 16(6):653–659
60. Gierlinger G, Sames-Dolzer E, Kreuzer M, Mair R, Zierer A, Mair R (2021) Surgical therapy of infective endocarditis following interventional or surgical pulmonary valve replacement. European Journal of Cardio-Thoracic Surgery
61. Dixon G, Christov G (2017) Infective endocarditis in children. Current Opinion in Infectious Diseases. 30(3):257–267
62. O'Donnell C, Holloway R, Tilton E, Stirling J, Finucane K, Wilson N (2016) Infective endocarditis following Melody valve implantation: comparison with a surgical cohort. Cardiology in the Young. 27(2):294–301
63. Van Dijck I, Budts W, Cools B, Eyskens B, Boshoff D, Heying R et al (2014) Infective endocarditis of a transcatheter pulmonary valve in comparison with surgical implants. Heart. 101(10):788–793
64. Albanesi F, Sekarski N, Lambrou D, Von Segesser L, Berdajs D (2014) Incidence and risk factors for Contegra graft infection following right ventricular outflow tract reconstruction: long-term results. European Journal of Cardio-Thoracic Surgery. 45(6):1070–1074
65. Ugaki S, Rutledge J, Aklabi M, Ross D, Adatia I, Rebeyka I (2015) An increased incidence of conduit endocarditis in patients receiving bovine jugular vein grafts compared to cryopreserved homograft for right ventricular outflow reconstruction. The Annals of Thoracic Surgery. 99(1):140–146
66. Gröning M, Tahri N, Søndergaard L, Helvind M, Ersbøll M, Ørbæk AH (2019) Infective endocarditis in right ventricular outflow tract conduits: a register-based comparison of homografts, Contegra grafts and Melody transcatheter valves. European Journal of Cardio-Thoracic Surgery. 56(1):87–93
67. Sharma A, Cote A, Hosking M, Harris K (2017) A systematic review of infective endocarditis in patients with bovine jugular vein valves compared with other valve types. JACC: Cardiovascular Interventions. 10(14):1449–1458
68. Dixon G, Christov G (2017) Infective endocarditis in children: an update. Curr Opin Infect Dis. 30(3):257–267
69. Wilson W, Taubert KA, Gewitz M, Lockhart PB, Baddour LM, Levison M et al (2007) Prevention of infective endocarditis: guidelines from the American Heart Association: a guideline from the American Heart Association Rheumatic Fever, Endocarditis, and Kawasaki Disease Committee, Council on Cardiovascular Disease in the Young, and the Council on Clinical Cardiology, Council on Cardiovascular Surgery and Anesthesia, and the Quality of Care and Outcomes Research Interdisciplinary Working Group. Circulation 116(15):1736–1754
70. NICE. Prophylaxis against infective endocarditis: antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures 2016 [Available from: https://www.nice.org.uk/guidance/cg64.
71. Thornhill MH, Dayer MJ, Forde JM, Corey GR, Chu VH, Couper DJ, Lockhart PB (2011) Impact of the NICE guideline recommending cessation of antibiotic prophylaxis for prevention of infective endocarditis: before and after study. Bmj. 342:d2392
72. Naik RJ, Patel NR, Wang M, Shah NC (2016) Infective endocarditis prophylaxis: current practice trend among paediatric cardiologists: are we following the 2007 guidelines? Cardiol Young. 26(6):1176–1182
73. Pharis CS, Conway J, Warren AE, Bullock A, Mackie AS (2011) The impact of 2007 infective endocarditis prophylaxis guidelines on the practice of congenital heart disease specialists. Am Heart J. 161:123–129
74. Schulz-Weidner N, Bulski JC, Siahi-Benlarbi R, Bauer J, Logeswaran T, Jux C, Wetzel WE, Krämer N (2020) Symptom-orientated oral hygiene for children after heart transplantation: Effectiveness of a standardized prophylactic program. Pediatr Transplant. 24(7):e13845
75. Johnson JA, Boyce TG, Cetta F, Steckelberg JM, Johnson JN (2012) Infective endocarditis in the pediatric patient: a 60-year single-institution review. Mayo Clin Proc. 87(7):629–635
76. Fisher RG, Moodie DS, Rice R (1985) Pediatric bacterial endocarditis. Long-term follow-up. Cleve Clin Q 52(1):41–45
77. Habib G (2006) Management of infective endocarditis. Heart. 92(1):124–130
78. Jomaa W, Ben Ali I, Abid D, Hajri Ernez S, Abid L, Triki F, Kammoun S, Gharbi A, Ben Rejeb O, Mahdhaoui A, Jeridi G, Azaiez MA, el Hraiech A, Ben Hamda K, Maatouk F (2017) Clinical features and prognosis of infective endocarditis in children: insights from a Tunisian multicentre registry. Arch Cardiovasc Dis. 110(12):676–681
79. Henaine R, Roubertie F, Vergnat M, Ninet J (2012) Valve replacement in children: a challenge for a whole life. Arch Cardiovasc Dis. 105(10):517–528
80. Robbins RC, Bowman FO Jr, Malm JR (1988) Cardiac valve replacement in children: a twenty-year series. Ann Thorac Surg. 45(1):56–61
81. Weinger M, Slagle J, Jain S, Ordonez N (2003) Retrospective data collection and analytical techniques for patient safety studies. Journal of Biomedical Informatics. 36(1-2):106–119
82. Baddour L, Wilson W, Bayer A, Fowler V, Bolger A, Levison M et al (2005) Infective endocarditis diagnosis, antimicrobial therapy, and management of complications: a statement for healthcare professionals from the Committee on Rheumatic Fever, Endocarditis, and Kawasaki Disease, Council on Cardiovascular Disease in the Young, and the Councils on Clinical Cardiology, Stroke, and Cardiovascular Surgery and Anesthesia, American Heart Association. Circulation 111(23)

Affiliations

Loay Eleyan[1] · Ameer Ahmed Khan[1] · Gledisa Musollari[2] · Ashwini Suresh Chandiramani[3] · Simran Shaikh[4] · Ahmad Salha[4] · Abdulla Tarmahomed[5] · Amer Harky[6,7]

[1] School of Medicine, Faculty of Health and Life Science, University of Liverpool, Liverpool, UK

[2] Imperial College London, Exhibition Road, South Kensington, London SW7 2BU, UK

[3] University of Glasgow, Medical school, University Avenue, G12 8QQ, Glasgow, UK

[4] St. Georges University of London, Cranmer Terrace, Tooting, London SW17 0RE, UK

[5] Department of Paediatric Cardiology, Alder Hey Children's Hospital, Liverpool, UK

[6] Department of Congenital Cardiac Surgery, Alder Hey Children Hospital, Liverpool, UK

[7] Department of Cardio-thoracic Surgery, Liverpool Heart and Chest Hospital, Liverpool, UK