

Infective endocarditis in children – lasting problem and growing incidence

Infekcyjne zapalenie wsierdza u dzieci – wzrastający problem

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Abstract

Infective endocarditis (IE) is becoming a more common illness in children, especially in patients with congenital heart disease. There remains no consensus as to the optimal diagnosis, treatment and prophylaxis. One of the most challenging problems in this group of patients is surgery, because of the often extremely small dimensions and the lack of proper valve prosthesis. In light of this growing problem, there is a need for better knowledge regarding IE if this insidious disease is to be promptly identified and effectively treated.

Key words: infective endocarditis, paediatric cardiac surgery, valve replacement, children

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Introduction

Over the last few decades, the epidemiology of infective endocarditis (IE) in the paediatric population has changed. In the 1970s roughly 30–50% of cases of IE in children were related to rheumatic heart disease [1], whereas nowadays congenital heart disease (CHD) is the most common reason for IE. Moreover, the increased frequency of IE is strongly connected with the increased survival rate among patients with CHD. The incidence of IE has been estimated to be approximately 0.05–0.12 cases per 1,000 paediatric admissions by different centres [2–5], while the figure reported from the USA is 0.43 cases per 100,000 children [3]. The increasing prevalence of IE in the paediatric population is associated with general immune deficiency, invasive devices, and innovative surgical procedures designed for complex cyanotic CHD, especially those associated with artificial material implantation, as well as

the complexity of comprehensive treatment in intensive care units. Nevertheless, 8–10% of cases of IE in children are not associated with CHD or any evident risk factor [6]. In such cases, IE usually affects the aortic or mitral valves and comes from *Staphylococcus aureus* bacteraemia [7].

Although the incidence of IE in children is lower than in adults, it is more difficult to treat. The lack of clear guidelines for the treatment of endocarditis in children makes it an even more complicated and problematic challenge.

Cardiac surgery and transcatheter procedures

Cardiac surgery and postoperative intensive care is an important independent risk factor for the development of IE. In particular, residual defects and surgical shunts contribute to damage of the endocardium and infiltration by bacteria. Those most susceptible to IE are cyanotic children after

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they have undergone corrective, palliative or physiological palliation surgery for CHD [8].

Although always possible, the risk of endocarditis in the first month after cardiac surgery is low. The risk usually rises as time goes by. IE can be a late complication of cardiac surgery for CHD, but unfortunately such a late occurrence is connected with rapid development and poor antibiotic response [9, 10].

Patients after transcatheter device implantation are also at risk of endocarditis, especially before the endothelialisation of the implants. The residual defects could be an additional risk factor for IE [11–13].

Pathogenesis

The interaction of two factors is necessary for IE to develop – endothelium damage and bacteraemia [14]. Turbulent flow (*i.e.* valvular disease, stenosis or regurgitation, residual shunt, recurrent stenosis) causes mechanical stress, which destroys the endothelium, followed by the deposition of platelets and fibrin, and finally the creation of nonbacterial thrombotic endocarditis (NBTE). NBTE is a perfect nidus for bacterial or fungal colonisation. Bacteraemia or fungemia can appear in the blood from any infection site, and even as a result of everyday activities such as brushing teeth or chewing food. The pathogens after nidus colonisation and multiplication cause a further adhesion of platelets and fibrin. In chronic cardiac patients, the endothelium surface is frequently damaged by catheters or pacing wires; endocarditis can also develop due to direct infection from implantable devices.

Diagnosis

Infective endocarditis is a difficult diagnostic problem, mostly because of its non-specific clinical symptoms. Clinical findings differ between neonates, children and adolescents. Infants with IE usually present feeding difficulties, tachycardia, respiratory disorders, hypotension, and a variety of neurological signs such as seizures, hemiparesis or apnoea. During physical examination, a new or changing heart murmur can be heard. However, in older children and adolescents, IE is associated with prolonged low-grade fever, fatigue, weight loss, weakness, arthralgias, myalgias and diaphoresis. In some cases, the symptoms of IE can develop rapidly with a high fever and progressive heart failure. These patients usually require urgent intervention, and the most likely aetiological factors are usually *Streptococcus pneumoniae* or *Staphylococcus aureus* [8, 10].

Due to its nonspecific clinical findings, endocarditis should be taken into consideration in every case of prolonged, nonresponding to antibiotics infection with fever, especially in children with congenital heart disease, and also in long

term follow-up after corrective surgery. Extracardiac findings such as petechiae, haemorrhages, Janeway lesions, Roth's spots or Osler nodes, are uncommon in children. The emboli of vessels in the abdominal viscera, in the heart, or in the brain, although rare, can be life threatening.

In clinical practice, a diagnosis of IE depends on proving a relationship between the signs of infection and echocardiographic changes on the endocardium. Both the European Society of Cardiology (ESC) and the American Heart Association (AHA) recommend using the Duke criteria for diagnosing IE in adults [15].

Modifications of the Duke criteria for children have been used in several studies, but because of the small number of patients, there remain doubts about their universal applicability [16, 17]. The Duke criteria are based on clinical, microbiological and echocardiographic findings (Table 1). The original Duke criteria have only 80% sensitivity in epidemiologic studies and less than 65% (63.2%) in clinical practice [18]. To improve the accuracy of diagnosis in adults, it is recommended to consider new imaging techniques such as multi-slice computer tomography (MSCT) and single-photon emission computed tomography/computed tomography (SPECT/CT) [19, 20]. These techniques have thus far no applications or certification in the paediatric population.

The gold standard of IE diagnosis is microbiological and histological examination of surgically excised tissue specimens such as valves, a damaged endocardium, or vegetations.

Imaging

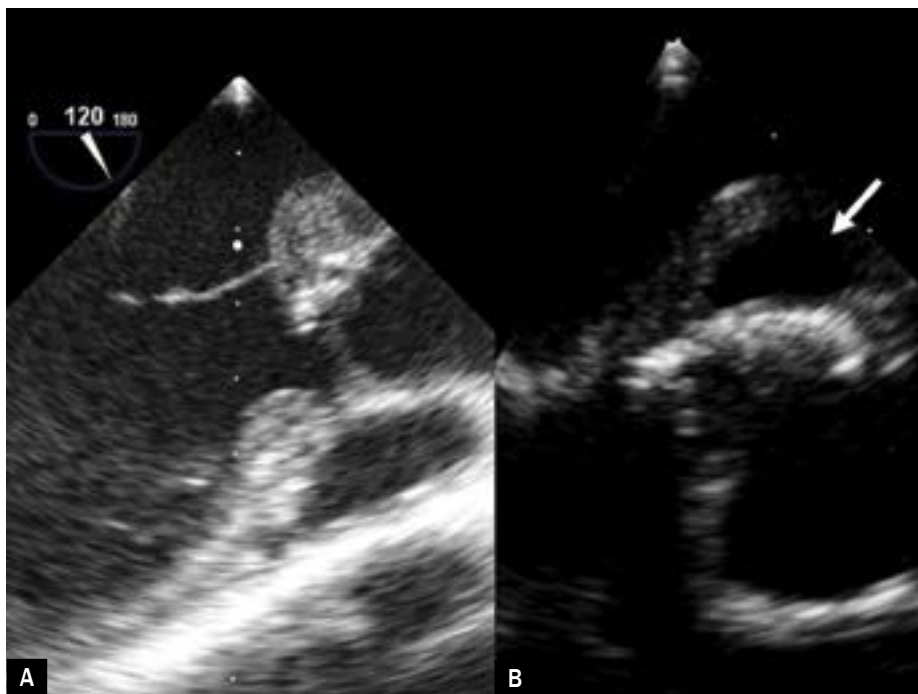
The most important imaging techniques in IE are transthoracic (TTE) and transoesophageal (TEE) echocardiography. Echocardiographic examination should be performed in every patient with a suspicion of IE [14]. It has an important role in diagnosis, evaluation of treatment, and monitoring of recurrence. In children, TTE is usually sufficient to visualise changes in the endocardium and dysfunction of the valves. TEE could be helpful in the evaluation of paravalvular leakage, left ventricle outflow tract complication, root abscesses, or endocarditis over a prosthetic valve (Figure 1). Those patients with chest deformations after surgery, trauma or congenital lesions, can also be better assessed with TEE.

Microbiology

Identifying the pathogen responsible for IE is very important, so it is crucial to take blood samples for microbiological examination as quickly as possible in every patient suspected of IE, especially where there is fever of an unexplained origin (FUO), a new heart murmur, a congenital diaphragmatic hernia (CDH), or a previous history of endocarditis. The process involves taking three blood cultures

Table 1. Modified Duke criteria for diagnosis of infective endocarditis in children (based on [15])

Major criteria
<p>1. Positive blood culture for IE:</p> <p>a) typical microorganism consistent with IE from ≥ 2 blood cultures:</p> <ul style="list-style-type: none"> • <i>Viridans streptococci</i>, <i>Streptococcus bovis</i>, or <i>HACEK group</i>; or • community-acquired <i>Staphylococcus aureus</i> or enterococci, in the absence of a primary focus; or <p>b) microorganisms consistent with IE from persistently positive blood cultures, defined as:</p> <ul style="list-style-type: none"> • ≥ 2 positive cultures of blood samples drawn > 12 h apart; or • all of three or a majority of ≥ 4 blood cultures, irrespective of the timing <p>c) 1 positive blood culture for <i>Coxiella burnetii</i> or antiphase-I immunoglobulin G antibody titre $> 1:800$</p> <p>2. Evidence of endocardial involvement:</p> <p>a) echocardiogram positive for IE (TEE recommended in prosthetic valves, rated at least possible IE by clinical criteria, or complicated IE; TTE as the first test in other patients) for IE, defined as:</p> <ul style="list-style-type: none"> • oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomic explanation; or • abscess; or • new partial dehiscence of prosthetic valve <p>b) new valvular regurgitation (worsening or changing of pre-existing murmur not sufficient)</p>
Minor criteria
<p>1. Predisposition: predisposing heart condition or IV drug use</p> <p>2. Fever: temperature $\geq 38.0^{\circ}\text{C}$</p> <p>3. Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages, and Janeway lesions</p> <p>4. Immunologic phenomena: glomerulonephritis, Osler nodes, Roth's spots, and rheumatoid factor</p> <p>5. Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with IE</p>

**Figure 1.** Transoesophageal echocardiography (TEE) in a 9 year-old boy with infective endocarditis caused by *Cardiobacterium hominis*. Periannular abscess (arrow) and vegetations attached to leaflets of aortic valve

by separate venous punctures on the first day of fever; if there is no growth after two days of incubation, another 2–3 blood samples should be taken.

Because of the relatively lower volume of circulating blood in children, the blood samples have to be smaller. In infants and younger children they should be limited to 1–3 mL, and 5–7 mL in older children. Bacteraemia is usually constant in IE, so there is no need to wait for pyrexia. Isolated growth in one sample should be taken into consideration with great care, due to the high possibility of contamination [15].

Most cases of IE are caused by the ‘big three’ pathogens – viridans group streptococci (VGS, like *Streptococcus sanquis*, *Streptococcus mitis* group, *Streptococcus mutans*), staphylococci (*Staphylococcus aureus*, coagulase-negative staphylococci), β -haemolytic streptococci and *Enterococcus* species (less common in children). Less common aetiological pathogens are microorganisms from the HACEK (*Haemophilus* species, *Aggregatibacter* species, *Cardiobacterium hominis*, *Eikenella corrodens* and *Kingella* species) group.

If fastidious organisms or unusual pathogens are suspected, the microbiological laboratory should be forewarned so that it can use longer incubation and more specific tests. From the age of 12 months onwards, the most common endocarditis pathogen in children with CHD is VGS. However, after cardiac surgery *S. aureus* and coagulase-negative staphylococci are more common [1, 6].

Culture-negative endocarditis

Up to 36% of patients with diagnosed endocarditis have negative blood cultures [21]. The reason behind a culture-negative endocarditis (CNE)-diagnosis is antibiotic therapy introduction before the collection of blood samples, or the need to make maximum efforts to search for organisms, which require more demanding conditions. Because of the nonspecific, slowly developing signs, the majority of patients are treated with antibiotics by a paediatrician or a general practitioner prior to IE being suspected.

Fastidious microorganisms, some bacteria and fungi, require more specific media and longer incubation times. Except for extended incubation, in some cases it is worth performing serological tests or using molecular techniques such as polymerase chain reaction (PCR) to detect RNA/DNA of the microorganisms [22].

The tests over surgically excised tissue can help to determine the aetiological factor behind IE, but they should be interpreted cautiously, because 13–55% of results are false-positive. Surgical materials remain positive for months after antibiotic therapy has begun, but unfortunately can detect microorganisms from previous episodes of endocarditis up to 12 years before surgery [22, 23].

Treatment

The treatment of IE consists of two complementary parts – antibiotic therapy and surgery. The immediate implementation of appropriate antibiotic therapy is extremely important for a successful outcome. Antibiotic therapy depends on having a diagnosed or suspected aetiological factor. There are different antibiotic strategies and durations of therapy, which usually lasts a minimum of 6–8 weeks. There are also therapeutic strategies for CNE, which should be re-evaluated as soon as a more precise diagnosis is made, i.e. after histological tests. Preoperative antibiotics therapy should be taken into account for the total duration of therapy, unless there is a need to change antibiotics based on blood cultures. Although there has been an improvement in IE treatment, the mortality rate is still 5–10% [15], and is higher in patients with previous heart disease.

Surgical treatment

The two major goals of surgical treatment of IE are to excise the infected tissues, and to restore the correct cardiac function.

The vegetations can cause valvular dysfunction, perianular progression of infection, sinus of Valsalva rupture, myocardial dysfunction, obstruction of conduits and shunts, pericardial effusion, coronary embolisation or dysfunction of artificial valves. Surgery is usually urgently required, especially in life-threatening conditions [24]. The most important indications for surgery are the progression of heart failure, uncontrolled infection, and emboli prevention.

Cardiac surgery for IE in children is an enormous challenge which grows more demanding the smaller the patient is. The first surgical challenge relates to the size of the patient. Even a fairly small vegetation on the valve or a periannular abscess can lead to resection of large cardiac structures or whole cusps of infected valve. The second basic problem of paediatric IE is the lack of proper valve prosthesis and materials to reconstruct cardiac morphology. There is no ‘paediatric’ size of artificial valve, either mechanical or biological. In addition, it should be remembered that no prosthetic valve has growth potential and a small prosthesis will have to be changed as the child grows. However, there have been promising initial reports on the use of a biological valve placed on a stent (Melody[®] valve; Figure 2) that could be percutaneously widened with balloons in the future [25].

It is vital to clear all current and suspected extracardiac sites of infection before cardiac surgery.

Prevention

Both the AHA and the ESC limit the use of antibiotic prophylaxis to patients with the highest risk for IE and patients

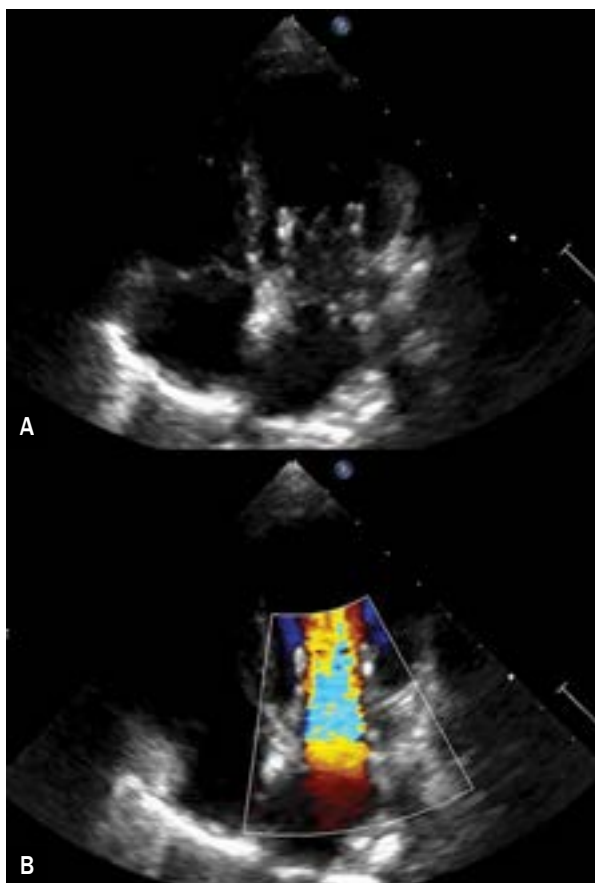


Figure 2A, B. Melody valve® in mitral position in a 3 year-old girl – 12 months after implantation because of acute mitral insufficiency in the course of infective endocarditis. There is possibility to percutaneous widen the diameter of the valve calibrated foramen in interatrial septum

with the highest risk for mortality or morbidity from IE. This is a consequence of the data that shows that up to 20% of IE could be associated with invasive procedures. Transient

bacteraemia appears during everyday activities such as brushing teeth or chewing food. The oral flora in children and adults differs, and changes with age. Nonetheless, dental hygiene and careful treatment of any oral infection should be undertaken [26].

The other issue is for a patient with CHD, particularly cyanotic heart disease. The presence of implanted foreign prosthetic materials such as patches, shunts or conduits, increases the risk of endocarditis, even many years after cardiac surgery. The AHA recommends antibiotic prophylaxis before high-risk dental procedures for all patients with unrepaired cyanotic CHD, as well as those individuals who underwent the repair of a CHD with prosthetic materials, or with diagnosed residual defects, and after percutaneous device implantation (for a period of six months). Particular attention should be paid to oral hygiene in children with cyanosis, who have specific periodontal concerns [27].

Conclusions

1. The growing number of children and adolescents with corrected CHD is the cause of the growing risk of IE. Therefore this particular group of patients should be treated by highly specialised teams familiar with congenital heart surgery.
2. There is a need for better knowledge about IE in children among general practitioners and paediatricians, as well as dentists, to provide a proper prophylaxis and shorten the time to diagnosis, introduce effective treatment, and improve outcomes.
3. The growing number of children suffering from IE should encourage progress in the field of prosthetic implantable materials that could minimise the risk of IE, while considering the potential to expand following children's growth.

Conflict(s) of interest

The author declares no conflicts of interests.

Streszczenie

Zachorowalność na infekcyjne zapalenie wsierdzia (IE) wzrasta w populacji dziecięcej, zwłaszcza u pacjentów z wrodzoną wadą serca. Właściwe postępowanie, diagnostyka, leczenie oraz właściwa profilaktyka pozostają przedmiotem wielu dyskusji. Leczenie chirurgiczne IE u dzieci stanowi szczególne wyzwanie, głównie z powodu małych rozmiarów pacjenta, konieczności zachowania potencjału do wzrostu i braku odpowiednich protez zastawkowych. W obliczu narastającego problemu należy zwiększać świadomość i propagować wiedzę o IE, żeby wcześniej rozpoznawać i skutecznie leczyć tę podstępą chorobę na wcześniejszych etapach.

Słowa kluczowe: infekcyjne zapalenie wsierdzia, kardiochirurgia dziecięca, zastawki, dzieci

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