INFECTIVE ENDOCARDITIS IN CHILDREN

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Infective Endocarditis (IE) is a microbial infection of the endocardium. It encompasses both bacterial and fungal infections, and also infection of the ductus arteriosus and surgically inserted shunts. Although it is less prevalent than in adults, the incidence in children has increased. Through improved medical technology, children with congenital heart disease are living longer in developed nations, so contributing to this increased incidence of IE. In developing countries, rheumatic heart disease remains the commonest substrate for infective endocarditis.

In developed countries, the majority of children who develop IE have underlying congenital heart disease. However, 10% do not; in such cases, the commonest culprit for IE is *Staphylococcus aureus*, which affects the aortic and mitral valves. Infective endocarditis was universally fatal in the pre-antibiotic era. In the current era, the fatality rate has been significantly reduced to 10%-25%. This reduction in mortality is attributable to a combination of appropriate antibiotic therapy, early detection, aggressive management of complications, and an improvement in surgical techniques.

Pathogenesis of infective endocarditis (Rohayati and Daniel, 2010; Hoen and Duval, 2013)

The pathogenesis of IE begins with endocardial injury, which is usually caused by hemodynamic and mechanical stress. Endocardial injury is a potent inducer of thrombogenesis–creating a fibrin-platelet deposition over the damaged endothelium. This fibrin-platelet deposit is sometimes termed 'non-bacterial thrombotic endocarditis' (NBTE).

Microorganisms from the bloodstream then colonize the altered endothelial surface and convert the NBTE to infective endocarditis, thus leading to the formation of the vegetation, a hallmark of IE. This vegetation has locally destructive effects, and can also cause embolization, focal infection, and host response related complications (Fig 1). Gram-positive organisms–Streptococci and *Staphylococcus aureus*–in particular have an affinity to damaging endothelium. When these pathogens colonize the damaged endothelium, they produce a further inflammatory response, triggering further platelet and fibrin deposition through cytokines and tissue factor activities (TFAs). The result is a large colony of bacteria buried within a fibrin/platelet mass, internalizing into the endothelium, and then secreting lysins, which have the potential to lyse endothelial cells, thus creating local damage.

Vegetations more commonly occur wherein blood is driven from a source of high pressure at high velocity into a low pressure 'sink', with the vegetation forming in the 'sink.' Areas of high pressure include the left ventricle and aorta, where blood flows through a narrow orifice. Areas of low pressure include the atria, pulmonary

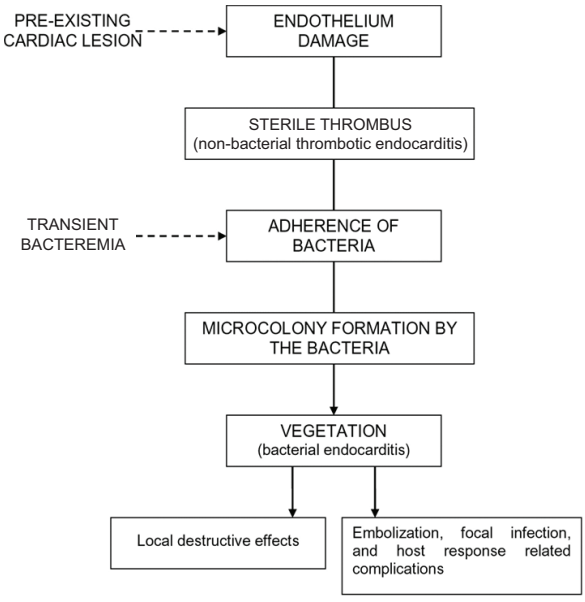

Fig 1–Pathogenesis of infective endocarditis.

trunk, and right ventricle. An example of this phenomenon is in the case of ventricular septal defects (VSD), where the vegetation occurs on the side of the low-pressure right ventricle.

Infective endocarditis can occur in both unoperated and operated congenital heart disease. In unoperated congenital heart disease, the most common lesions are those where the blood flows at a very high velocity and causes extreme turbulence, for example, small ventricular septal defect (VSD), aortic stenosis, aortic regurgitation, and patent ductus arteriosus (PDA). It can also occur in the setting of prolapsed mitral valve with mitral regurgitation and hypertrophic cardiomyopathy with left ventricular outlet tract obstruction. Due to the low-velocity shunt within a secundum ASD, IE is rare in this malformation.

Cardiac surgery can eliminate the potential for infective endocarditis if the lesion is completely repaired. For example, following the complete repair of a VSD or PDA with no sequelae, the risk of IE is reduced to that of the normal population by 6 months post surgery. Conversely, cardiac surgery has the propensity to increase risk of IE; this is the case following the insertion of conduits, shunts, and replacement of valves with prostheses, where hemodynamics are more distorted than before surgery.

The most common pathogens in IE are gram-positive bacteria, such as *Streptococcus viridians* and *Staphylococcus. Staphylococcus aureus* is mostly associated with virulent, acute bacterial endocarditis and normal valves, whereas *Staphylococcus epidermidis* is more associated with indwelling catheters and prosthetic materials, usually in the right heart. *Enterococcus* is less common in pediatric IE compared to adults. Prior to the antibiotic era, *Streptococcus pyogenes* was a devastating cause of IE, particularly after an episode of erysipelas, but that has now become rare. *Streptococcus pneumoniae* is still seen as a cause of IE in children. Gram-negative organisms have less affinity to damage the endothelium and are rarely a cause of IE. There have been studies that have shown that the viridans group of Streptococci are the commonest bacterial pathogens in IE, followed by *Staphylococcus aureus*, coagulase-negative Staphylococci, and *Streptococcus pneumoniae.*

The incidence of fungal endocarditis is increasing because of medical technology and longer stays in intensive care associated with invasive medical interventions. Examples of such situations are with pro-

longed catheterization, antibiotics, dialysis, hyperalimentation, and surgical intervention with insertion of prosthetic material. Fungal IE is usually caused by Candida, and occasionally also by Aspergillus. It is associated with 75% mortality and high complication rates. The diagnosis is often difficult to make, and therefore delayed, further compounding its high complication rates.

Clinical manifestations of infective endocarditis (Rohayati and Daniel, 2010; Hoen and Duval, 2013)

As in adults, the clinical symptoms and signs of IE in children are due to four factors: bacteremia, valvulitis, the immunological response to the infection, and embolic phenomena. Features in children can also be classified into acute and subacute presentations. However in reality, the presentation is often non-specific and highly variable in children.

Clinicians should maintain a high index of suspicion for IE in children who have had cardiac surgery with residual sequelae, have prosthetic valves, indwelling catheters, implantable devices, and conduits. Fever is the most common symptom; this can be high grade in cases of *Staphylococcus aureus* and tends to be low-grade in cases of subacute bacterial endocarditis (SBE). There can also be other somatic complaints, including fatigue, weakness, arthralgias, myalgias, anorexia, weight loss, rigors and diaphoresis. Arthralgias and arthritis are more common in SBE. The child may present in congestive cardiac failure and valvulitis, embolization to the coronary circulation causing myocardial infarction, and may also present with diffuse myocarditis. The symptoms of embolization of infected material very much depend on where the material is embolized. Vegetations from the left heart can embolize to anywhere in the body, leading to ischemia, infarction, or mycotic aneurysms. Embolization of infected material from right heart endocarditis can lead to chest pain or breathlessness, and may even be misdiagnosed as pneumonia. Embolization from the left side of the heart causing splenic infarction may present as an acute abdomen. Other clinical features include neurological complications, such as stroke, confusional states, multiple brain abscesses and headaches, as well as renal abnormalities, such as hematuria, glomerulonephritis, or renal infarction with *Staphylococcus aureus*.

Physical findings of children with infective endocarditis are also highly variable. The majority will have fever–some will be anemic and may also exhibit clinical features of pre-existing heart disease. It is important to frequently examine a child in whom IE is suspected to look for a changing murmur. The classical extracardiac manifestations of IE in adults such as petechial hemorrhages, Janeway lesions, and Osler's nodes are rarely seen in children.

In newborns, IE may also occur–usually in cases with a structurally normal heart. It most typically occurs in premature babies after prolonged stays in the neonatal ICU with long-term insertion of indwelling catheters, therefore leading to right sided endocarditis. As with older children, the presentation is often non-specific, including feeding difficulties, respiratory distress, cardiac failure, and septicemia. Therefore, it is a diagnosis that is easily missed unless there is a high index of suspicion.

Diagnosis of infective endocarditis (Rohayati and Daniel, 2010; Hoen and Duval, 2013)

The gold standard of making the diagnosis of IE is blood cultures. The hallmark of bacteremia in IE is demonstration of a continuous bacteremia via 2-3 sets of blood cultures. The identity of the organism is very important, because it may suggest the source of the bacteremia and also guide appropriate antibiotic therapy. It is not necessary to take blood culture samples with the fever cycle. If blood cultures are negative, but the clinician is still highly suspicious of endocarditis and there is prior use of antibiotics, antibiotic therapy should be held for at least two days before repeating the blood cultures.

Other laboratory investigations may also be helpful, such as antibiotic sensitivities, the minimum inhibitory concentration (MIC) value, the full blood count that may demonstrate anemia or neutrophilia, urinalysis, which may demonstrate microscopic hematuria, or glomerulonephritis, or raised erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP).

With regards to imaging, echocardiography is the mainstay in diagnosis of IE and visualization of vegetations. It also plays an important role in following the progression of the disease and the disease outcome with respect to complications.

Although in adults transesophageal echocardiography is the gold standard for imaging in IE, this is usually not necessary in children in which transthoracic echocardiography has a higher sensitivity. Transesophageal echocardiography is usually reserved for cases that have poor echo windows, and involvement of aortic valves where an aortic root abscess is suspected. However, there are limitations of echocardiography – the absence of vegetations on an echocardiogram does not rule out infective endocarditis. Other types of echogenic masses may also resemble vegetations, such as sterile thrombi. The role of MRI and CT in the diagnosis of IE is very limited due to the difficulty in acquiring images, their inability to evaluate motion, and motion artifact. However, it may be useful in managing endocarditis involving the aortic arch.

Because IE is a mimicker of many diseases, it is often difficult to make a diagnosis. The most validated criteria for use in children is the Modified Duke's criteria for diagnosis of infective endocarditis (Fig 2). It looks at both microbial evidence of the disease on blood cultures, as well as other evidence of endocardial involvement.

Case examples

Case study 1. A 7-year-old girl presented with fever and rash. The blood cultures grew *Staphylococcus aureus*. She was admitted to hospital, and it was then noted after a few days that her femoral pulses were diminished. Urgent MRI demonstrated that there was a previously unrecognized shelf in the aortic arch, and beyond this, there was distal irregularity, which was later found to be an abscess of the aortic arch (Fig 3). The child was immediately sent for surgery.

Case study 2. An 8-year-old girl, with history of repair of the aortic and mitral valves, presented to the hospital with symptoms of pneumonia 1 year later. Three successive sets of blood cultures revealed *Streptococcus pneumoniae* sensitive to amoxicillin/clavulanic acid. Amoxicillin/clavulanic

Major criteria:

Blood culture positive for infective endocarditis

- Typical microorganisms consistent with infective endocarditis from 2 separate blood cultures: viridans streptococci, *Streptococcus bovis*, HACEK group. *Staphylococcus aureus*; or community-acquired enterococci in the absence of a primary focus; or
- Microorganisms consistent with infective endocarditis from persistently positive blood cultures defined as follows: at least two positive cultures of blood samples withdrawn > 12 h apart or all of 3 or a majority of 4 separate cultures of blood (with first and last sample withdrawn at least 1 h apart).
- Single blood culture positive for *Coxiella burnetii* or anti-phase 1 IgG antibody titer > 1 : 800

Evidence of endocardial involvement

- Positive echocardiogram (transesophageal echocardiograpy [TEE] recommended in patients with prosthetic valves, meeting criteria for possible IE by clinical criteria or complicated IE [paravalvular abscess]. Transthoracic echocardiogram [TTE] as first in all diagnosis)
  - Oscillating intracardiac mass on valve or supporting structure 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
  - New valvular regurgitation (worsening or changing or preexisting murmur not sufficient).

Minor criteria:

- Predisposition, predisposing heart condition, or IDU
- Fever (temperature >38°C)
- Vascular phenomena, major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, and Janeway lesions
- Immunologic phenomena; glomerulonephritis, Osler nodes, Roth spots, and positive rheumatoid factor
- Microbiological evidence: positive blood culture but does not meet a major criterion as noted above or serologic evidence of active infection with organism consistent with infectious endocarditis

Definite:

- 2 major criteria OR 1 major and 3 minor criteria OR 5 minor criteria

Possible:

- 1 major and 1 minor criterion OR 3 minor criteria

Rejected:

- Firm alternative diagnosis OR resolution of syndrome after 4 days of antibiotic therapy OR does not meet criteria above

Key: HACEK, *Haemophilus* species, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens*, and *Kingella* species; IDU, injection drug use.;

Fig 2–Modified Duke criteria for diagnosis of infective endocarditis.

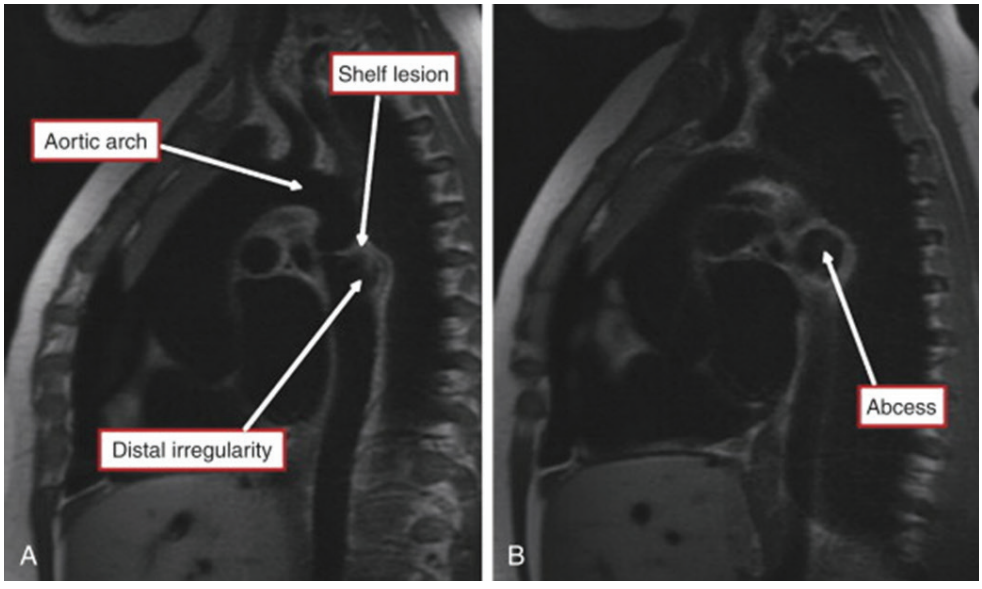

Fig 3–Magnetic resonance imaging of a 7-year-old girl which demonstrates (A) shelf in the aortic arch and (B) abscess of the aortic arch.

acid was administered, but the patient developed heart failure after treatment. On echocardiogram, the patient's mitral valve appeared thickened with severe regurgitation. This supported the diagnosis of infective endocarditis caused by *Streptococcus pneumoniae* infection that had affected the child's mitral valve. Unfortunately, the patient died, as it was not possible to operate on this lesion.

Case study 3. A 2-month-old baby returned from Kuala Lumpur having had surgery for a ventricular septal defect (VSD) closure and an aortic arch repair. The child had persistent bacteremia, which was found on blood culture to persistently be methicillin resistant *Staphylococcus aureus*. Echocardiogram revealed a vegetation on the right ventricular aspect of the VSD patch and around the tricuspid valve. The child was treated with a prolonged course of antibiotics, after which the vegetations appeared to be resolving. However, the child's VSD patch dehisced, and the team was unable to send the child for surgery. The child developed fulminant heart failure and subsequently died.

Management of infective endocarditis (Rohayati and Daniel, 2010; Hoen and Duval, 2013)

The principle of medical management of IE is the prolonged use of appropriate antibiotics. This must be taken using a multidisciplinary team approach, with early and on-going consultation between cardiologists, microbiologists, infectious disease specialists, and cardiothoracic surgeons. Surgical therapy may be deemed appropriate in certain cases. Blood cultures must be taken before antibiotics are given in suspected cases of endocarditis. Treatment is guided by blood cultures and sensitivities. If the patient is stable, antibiotics may be delayed pending culture results. However, if the child is acutely ill, three cultures may be taken and antibiotics immediately started. Empiric treatment should cover both *Staphylococcus* and *Streptococcus*. Within vegetations, there are organisms in high concentration within the mixture of fibrin and platelets, which are very resistant to host defense mechanisms. Antibiotic therapy is therefore prolonged for up to 4 to 8 weeks. Concentrations of antibiotics within the vegetation need to be high and sustained to exert therapeutic effects, necessitating use of the parenteral route. Use of bactericidal drug is important to prevent relapse, and therapeutic drug levels should be monitored. Blood cultures should be repeated after treatment is commenced to assess response to treatment. With respect to fungal endocarditis, it is recommended that amphotericin B is given for 6 weeks; however, antifungals often do not penetrate vegetations well, and surgery is often needed.

Many IE cases are associated with complications, and some patients will need surgery in addition to medicine to manage their disease. Indications for surgery in children are not as clear-cut as adults, and the decision for surgery is often individualized in each case. In general, indications for surgery are severe uncontrolled heart failure, persistent or severe infection and fungal endocarditis, endocarditis in surgically created shunts or conduits, infected patches or intracardiac devices, and vegetations larger than 1 cm, which may increase the risk of embolism.

It cannot be emphasized enough the importance of the multidisciplinary ap-

proach to the management of infective endocarditis, as well as the early and ongoing involvement of all team members. Cardiologists have attempted several ways to try to prevent IE, and through 50 years of American Heart Association (AHA) Guidelines, antibiotic prophylaxis was advocated. However, there is lack of strong evidence for its use, and it is now known that IE is more likely to result from frequent exposure to random bacteremias associated with daily activities, than the association with dental therapy. Currently, the risk of antibiotic associated adverse events is considered to exceed benefits, if any, from prophylactic antibiotic therapy. The 2008 NICE guidelines removed all indications for antibiotic prophylaxis in the prevention of IE, while the 2007 AHA guidelines have been slightly more cautious with such guidance. In any case, the most important factor to advise patients of in the prevention of IE is dental hygiene and regular dental visits.

REFERENCES

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