Infectious endocarditis

A. Carceller

Department of Pediatrics. CHU Sainte-Justine. Université de Montréal. Montréal. Canada.

Why the Tenth Symphony of Gustav Mahler was Unfinished?

Gustav Mahler[1,2] was born on July 7, 1860, in Kalista (Bohemia) near Moravia. His first musical work was a polka composed at the age of 6 years. Mahler studied music at the Vienna Conservatory. He was a composer much criticized by the press. In 1902, Mahler married Alma Schindler, with whom he had 2 daughters, Anna and Maria. The latter died of scarlet fever at the age of only 5. The death of his younger daughter left him depressed; that same year, he discovered he had a heart disease. Forced by a largely anti-Semitic press, he accepted an offer to conduct the Metropolitan Opera in New York in 1907. In 1911, he fell seriously ill with endocarditis. He was attended by Dr. E. Libman who demonstrated the presence of Streptococcus viridans *in a large volume (200 ml) of his blood. Mahler was taken to Paris and treated with* "Metchnikoff's Bulgarian milk" (Lactobacillus bulgaricus), *the probiotics of that era. However, septic abscesses began to appear in other parts of his body. He was taken back to Vienna, and died on May 18, 1911, leaving his Tenth Symphony incomplete.*

INTRODUCTION

Infectious endocarditis is a major infection involving the endocardium, particularly the cardiac valves. For a long time, it was called bacterial endocarditis. Actually, in addition to bacteria, infectious endocarditis can be caused by other microbiological agents. Changes in the presentation of this disease are explained by modifications in susceptible populations, predisposing factors, and the evolution of microorganisms. Despite a great deal of progress made in recent decades, the diagnosis and treatment of endocarditis continue to be difficult.

HISTORICAL ASPECTS

Fernel's *Medicini* in 1554 was the first book to introduce the term of endocarditis[3]. During the 17th and 18th centuries, anomalies of the cardiac valves were described during autopsies of these patients[2]. In 1669, Richard Lower in England was the first to diagnose endocarditis of the tricuspid valve. In 1806, Jean Nicolas Corvisart (1755-1821) was probably the first to use the term "vegetations"[2]. In 1816, Théophile Laënnec[1] invented the cylindrical stethoscope, improving cardiac auscultation. In 1835, Jean-Baptiste Bouillaud[2] defined the endocardium in his "*Traité clinique des maladies du coeur*". In France, routine blood cultures were introduced by Pasteur in the late 19th century[1]. Penicillin was discovered by Sir Alexander Fleming in 1929 and it has being administered for the treatment of this disease since 1940[2].

EPIDEMIOLOGY

Currently, the incidence of endocarditis is 1-4 cases/100,000 or 1/1,300 annual paediatric admissions[4,5]. The increased occurrence of endocarditis is related to improved survival of children with congenital heart disease, newborns or other very ill children. Vascular conduits, patches or valvuloplasty in children with congenital heart disease are risk factors for endocarditis[6]. Other risks are: catheter use in critically ill children, children with immunodeficiency, and the neonatology and the paediatric intensive care units[7]. Eight to 10 percent of paediatric infectious endocarditis cases occur in healthy hearts. Endocarditis caused by intravenous drug use is rare in paediatrics. In the past, rheumatic fever was a risk factor, but it has disappeared in the western world. The epidemiology of endocarditis also has changed, thanks to the development and evolution of paediatric cardiology.

PATHOGENESIS

An injury in the endotelium is the first inducer of thrombogenesis[4], allowing bacteria to adhere and form vegetation. In children with cardiac malformations and turbulent or abnormal blood flow, injuries to the endothelium can easily arise. Catheters traumatize the endocardium[8]. Cutaneous or mucosal injuries from tracheal suction, parenteral feeding and umbilical or peripheral

Correspondence: Ana Carceller MD
Department of Pediatrics. CHU Sainte-Justine.
3175 Chemin Côte Ste-Catherine.
Montréal. Québec
H3T 1C5 Canada.
E-mail: ana_carceller@ssss.gouv.qc.ca

catheters are at the origins of bacteraemia in newborns[4]. Neonatal endocarditis frequently affects the right heart of newborns. If there is a critical mass of bacteria in the blood during bacteraemia, they can propagate and adhere to the endocardium. During thrombogenesis, blood platelets, sanguinous fibrin and blood cells collect as deposits, and an aseptic thrombus is formed. Bacteria colonize the aseptic thrombus, and blood platelets, fibrin and blood cells are deposited over these organisms, creating vegetation. Microorganisms trapped in the vegetation are protected from phagocytes and other defence mechanisms[4].

Clinical manifestations

The presentation can be insidious with prolonged fever and non-specific symptoms: fatigue, weakness, anorexia, weight loss, and sweating. At other times, it can be sudden, and these children are terribly ill. Endocarditis presents 4 phenomena:

1. Bacteraemia or fungemia.
2. Valvulitis: new heart murmur or cardiac insufficiency.
3. Immunological responses, much less frequent in children than in adults: petechias, haemorrhages, injuries of Roth or Janeway, Osler nodules or splenomegaly.
4. Embolic phenomena may involve the kidneys, abdominal viscera, brain or heart.

In newborns, the presentation is non-specific. Septic emboli are frequent, causing: osteomyelitis, meningitis or pneumonia[4].

Etiology and Laboratory data

Blood culture is indicated in all children with fever of unknown origin, pathological murmur, a history of cardiac malformation or antecedents of endocarditis. During endocarditis, bacteraemia is continuous; therefore, blood cultures can be done at any time[9]. It is important to collect an adequate amount of blood; in small children, this can vary from 1 to 3 ml, and in older children, 5-7 ml. Three blood cultures[4,5] detect more than 95% of endocarditis in children not exposed to antibiotics, and 90% in children who have received antibiotics[10-13].

Most agents which cause endocarditis are gram-positive cocci[14]: *Streptococci*, *Staphylococci*, *Enterococci*. The organisms most frequently detected in infectious endocarditis are the *S. viridans* and the *S. aureus*[4]. In endocarditis caused by catheters, the *S. aureus* and the *Staphylococci* coagulase-negative are frequent. In addition to those 2 agents, it is necessary in newborns to include the presence of *Candida*, *Klebsiella* and *Enterobacter*[14]. The organisms classified as the HACEK group are less frequently found at a paediatric age: *Haemophilus parainfluenzae*, *H. aphrophilus*, *H. paraphrophilus*, *H. influenzae*, *Actinobacillus actinomycetemcomitans*, *Cardiobacterium hominis*, *Eikenella corrodens, Kingella Kingae* and *K. denitrificans*[4]. Fungi are represented by *Candida* and *Aspergillum*. Mylonakis et al[15] enumerated the percentage of microbiological agents detected according to patient age (table 1).

Endocarditis is diagnosed despite negative blood culture if clinical symptoms and heart ultrasound show evident signs of infection. The incidence of negative blood culture is approximately 5-7%, mostly occurring in patients taking antibiotics or in endocarditis produced by pathogens other than bacteria[4,16]. Vegetation culture can help in the diagnosis[16]. Other laboratory results are non-specific: anaemia, leucocytosis, abnormal sedimentation rate, protein C-reactivity, hyper-gammaglobulinaemia, haematuria, proteinuria.

TABLE 1. **Pathogens causing endocarditis according to age**

Pathogen	Neonates (%)	2 months-15 years (%)
Streptococci spp	15-20	40-50
Staphylococcus aureus	40-50	22-27
Coagulase-negative *staphylococci*	8-12	4-7
Enterococcus spp	< 1	3-6
Gram-negative bacilli	8-12	4-6
Fungi	8-12	1-3
Culture negative and HACEK organisms*	2-6	0-15
Polymicrobial	3-5	< 1

*HACEK: *(Haemophilus parainfluenzae, H. aphrophilus, H. paraphrophilus, H. Influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella Kingae, K. denitrificans)*
Adapted from Mylonakis et al[15].

Echocardiography

For more than 15 years, heart ultrasound has been revolutionizing the diagnosis of endocarditis. This technique visualizes the place of infection, the vegetation, the extent of injury to the valves, and cardiac function. It also evaluates disease severity and influences medical or surgical treatment decisions. Doppler ultrasound allows the diagnosis of stenosis and valve insufficiency. Transthoracic echocardiography, with a sensitivity of 81%, is very helpful in the diagnosis of paediatric endocarditis[16]. Transoesophagic echocardiograpahy is employed less often in children, and frequently if transthoracic echocardiography is incapable of detecting vegetation[17-19]. However, the absence of vegetation does not exclude the diagnosis of endocarditis. Endocarditis affects the valves, but it can also be located in a defect of the septum, the tendinous cords or wall of the endocardium.

The diagnosis of endocarditis is difficult[20] as its clinical manifestations are numerous and non-specific. This explains why the differential diagnosis of endocarditis is important. Considering the consequences of misdiagnosed

endocarditis, false-positives do occur. In countries with high immigration rates, it is necessary to remember that recurrence of rheumatic fever can present with the same clinics as endocarditis[21,22]. Echocardiography in conjunction with clinical suspicion is the best criterion for the diagnosis of endocarditis.

CRITERIA FOR DIAGNOSIS

In 1909, Sir Thomas Horder[1] from England described the first criteria for diagnosis: the signs and symptoms of endocarditis. Throughout the 20th century, these criteria have undergone various modifications. In 1981, Von Reyn et al[23] (table 2) proposed criteria to facilitate the diagnosis of the disease. These authors presented 123 adults treated at the Beth Israel Hospital in Boston and classified endocarditis as: definitive, probable, possible, or rejected. In 1994, at Duke University in North Carolina, Durack et al[24] (tables 2 and 3) proposed new diagnostic criteria with the introduction of echocardiography: definitive, possible or rejected endocarditis. According to the criteria of Durack[24] et al, any case of endocarditis not rejected must be considered possible. These criteria seem to present good sensitivity, but are non-specific. In 2000, Li et al[25] (tables 2 and 3) tried to be stricter in endocarditis diagnosis and modified the earlier criteria of Durack[24] et al.

The above-mentioned diagnostic criteria have been validated for use in adult cardiology[26]. Some authors have tried to validate these criteria in paediatric cardiology[27-29]. However, infectious endocarditis is a disease with a very variable clinical presentation. Isolated criteria are not sufficient to make a diagnosis. The various criteria are clinical guides to help in the diagnosis, but they do not replace clinical judgement. Molecular diag-

TABLE 2. **Criteria for diagnosis**

The Von Reyn Criteria[23] (1981)	Duke Criteria[24] (1994)	Li Criteria[25] (2000)
Definite Infective Endocarditis Direct evidence of infective endocarditis based on histology from surgery or autopsy or on bacteriology of vegetation or embolus	**Definite Infective Endocarditis** *Pathologic criteria* Microorganisms: demonstrated by culture or histology in a vegetation or in a vegetation that has embolized or in an intracardiac abscess or Pathologic lesions: vegetation or intracardiac abscess, confirmed by histology showing active endocarditis *Clinical Criteria* listed in table 3: – 2 major criteria, or – 1 major and 3 minor criteria, or – 5 minor criteria	**Definite Infective Endocarditis** *Pathologic Criteria* Microorganisms: demonstrated by culture or histologic examination of a vegetation, a vegetation that has embolized or an intracardiac abscess or Pathologic lesions: vegetation or intracardiac abscess confirmed by histologic examination *Clinical Criteria* listed in table 3: – 2 major criteria, or – 1 major and 3 minor criteria, or – 5 minor criteria
Probable Infective Endocarditis Persistently positive blood cultures plus one of the following: – New regurgitant murmur – Predisposing heart disease and vascular phenomena Negative or intermittently positive blood cultures plus three of the following: – Fever – New regurgitant murmur – Vascular phenomena		
Posible Infective Endocarditis Persistently positive blood cultures plus one of the following: – Predisposing heart disease or – Vascular phenomena Negative or intermittently positive blood cultures with all three of the following: – Fever – New regurgitant murmur – Vascular phenomena For *viridans streptococcal* cases only: at least two positive blood cultures without an extra-cardiac source and fever	**Possible Infective Endocarditis** Findings consistent with infective endocarditis that fall short of Definite but not rejected	**Possible Infective Endocarditis** – 1 major criterion and 1 minor criterion, or – 3 minor criteria
Rejected Infective Endocarditis Alternative diagnosis Empiric antibiotic therapy warranted Culture negative endocarditis diagnosed clinically, but excluded by postmortem	**Rejected Infective Endocarditis** Firm alternate diagnosis, or Resolution of manifestations, with antibiotic therapy for 4 days or less, or No pathologic evidence of endocarditis at surgery or autopsy, after antibiotic therapy for 4 days or less	**Rejected Infective Endocarditis** Firm alternate diagnosis, or Resolution of manifestations with antibiotic therapy for ≤ 4 days, or No pathologic evidence of endocarditis at surgery or autopsy with antibiotic therapy for ≤ 4 days, or Does not meet criteria for possible infective endocarditis

Adapted from[23-25].

TABLE 3. **Criteria for diagnosis**

Duke Criteria[24] (1994)	Li Criteria[25] (2000)
Major Criteria	**Major Criteria**
Positive blood culture	*Positive Blood Culture*
Typical microorganism for endocarditis from two separate blood cultures: – *Viridans streptococci*, *Streptococcus bovis,* HACEK group*, or – *Staphylococcus aureus or enterococci*, in the absence of a primary focus, or	Typical microorganisms from two separate blood cultures – *Viridans streptococci*, *Streptococcus bovis,* HACEK group*, *Staphylococcus aureus,* or – *Enterococci* in the absence of a primary focus, or
Persistently positive blood culture, defined as recovery of a microorganism from: – Blood cultures drawn more than 12 hours apart, or – All of three or a majority of four or more separate blood cultures, with first and last drawn at least 1 hour apart	Microorganisms from persistently positive blood cultures: – At least two positive cultures of blood samples drawn > 12 hour apart, or – All of three or a majority of ≥ 4 separate cultures of blood with first and least sample drawn at least 1 hour apart – Single positive blood culture for *Coxiella burnetti* or antiphase I Ig G antibody titer > 1:800
Evidence of endocardial involvement	*Evidence of endocardial involvement*
Positive echocardiogram: – Oscillating intracardiac mass, on valve or structures, or in the path of regurgitant jets, or on implanted material, or – Abscess, or – New partial dehiscence of prosthetic valve, or New valvular regurgitation	Positive Echocardiogram. Transesophageal echocardiography recommended in patients with prosthetic valves, rated at least possible endocarditis by clinical criteria, or complicated endocarditis; transthoracic echocardiography as first test in other patients, defined as follows: – Oscillating intracardiac mass on valve or structures, in the path of regurgitant jets, or on implanted material, or – Abscess, or – New partial dehiscence of prosthetic valve New valvular regurgitation
Minor Criteria	**Minor Criteria**
Predisposing heart condition or intravenous drug use Fever ≥ 38 °C Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor Positive blood culture but not meeting major criterion Echocardiogram consistent with endocarditis but not meeting major criterion	Predisposing heart condition or injection drug use Fever ≥ 38 °C Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages, Janeway's lesions Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor Positive blood culture but not meeting major criterion Echocardiographic minor criteria eliminated

*HACEK: *Haemophilus species, Actinobacillus (Haemophilis) actinomycetemcomitans, Cardiobacterium hominis, Eikenella species* and *Kingella kingae.*
Adapted from [24,25].

TABLE 4. **Therapy of Infectious Endocarditis**[4,6]

Streptococci, Enterococci			
– Penicilin G plus	200.000 U IV	q 4-6 h	4-6 weeks
– Gentamicin*	3 mg IM or IV	q 8 h	2-6 weeks
Allergic to penicillin:			
– Vancomycin	40 mg IV	q 6-12 h	4-6 weeks
– ± gentamicin*	3 mg IM or IV	q 8 h	2-6 weeks
Staphylococci			
– beta-lactamase resistant penicillin	200 mg IV	q 4-6 h	6 weeks
– ± gentamicin*	3 mg IM or IV	q 8 h	3-5 days
Allergic to penicillin			
– Vancomycin	40 mg IV	q 6-12 h	6 weeks
– ± gentamicin*	3 mg IM or IV	q 8 h	2 weeks

*Dose of gentamicin should be adjusted to achieve peak and through concentration in serum of approximately 3.0 and < 1.0 μg of gentamicin/ml.
Adapted from Ferrieri[4] and Danilowicz[6].

nosis can be helpful in cases with negative blood culture[30]. Echocardiography also has been very useful. In the paediatric population, transthoracic echocardiography gives considerable information; transoesophagic echocardiography is rarely necesary[17-19]. Echocardiography is not indicated if there is no clinical evidence to support the diagnosis of endocarditis. Each patient with suspicion of endocarditis deserves critical evaluation, to improve the clinical-microbiological diagnosis and treatment[31].

TREATMENT

In general, treatment is given for 4 weeks, but is extended up to 6 weeks if the symptoms of presentation have lasted more than 3 months (table 4)[4,6,15,32]. Treatment is initiated in the hospital, but in some cases, it is complemented with antibiotic therapy at home.

TABLE 5. **Risk for complications**

Complications of Infectious Endocarditis[4]
Congestive heart failure
Emboli: cerebral, pulmonary, renal, coronary
Periannular abscess
Arrythmia or new heart block
Valvular dehiscence or graft or shunt occlusion
Persistent bacteremia or fungemia
Metastatic infection
Mycotic aneurysms
Glomerulonephritis or renal failure

High risk for complications for infective endocarditis[31]
Prosthetic cardiac valves
Left side infective endocarditis
Staphylococcus aureus endocarditis
Fungal endocarditis
Previous infective endocarditis
Prolonged clinical symptoms > 3 months
Cyanotic congenital heart disease
Patients with systemic to pulmonary shunts
Poor clinical response to antimicrobial therapy

Echocardiographic features suggesting potential surgical intervention[4]
Vegetation:
– > 10 mm
– ≥ 1 embolic event during first 2 weeks of therapy
– ≥ 2 emboli during or after therapy
– Increase in vegetation size after 4 weeks of therapy
Valvular dysfunction:
– Aortic or mitral insufficiency
– Heart failure
– Valve perforation or rupture
Perivalvular extension:
– Valvular dehiscence, rupture or fistula
– New heart block
– Large abscess or extension of abscess

Adapted from[4,31].

TABLE 6. **Prophylaxis of endocarditis**

Cardiac conditions associated with infectious endocarditis and prophylaxis recommendations[4-6,34-38]
High risk:
– Complex cyanotic heart diseases (single-ventricle, transposition of great arteries, tetralogy of Fallot)
– Aortic valve lesion or coarctation of the aorta, mitral stenosis or regurgitation, ventricular septal defect
– Prostheses or homograft
– Shunts or conduits
– Previous endocarditis
– Previous rheumatic heart disease with valvular dysfunction

Moderate risk:
– Other congenital cardiac malformations, other than above (except ASD)
– Acquired valvular dysfunction (rheumatic heart disease)
– Hypertrophic cardiomyopathy
– Mitral valve prolapse with valvular regurgitation

Endocarditis prophylaxis not recommended[4-6,34-38]
Atrial septal defect
Surgical repair of atrial septal defect, ventricular septal defect or patent ductus arteriosus
Mitral valve prolapse without valvular regurgitation
Innocent heart murmur
Previous Kawasaki disease without valvular dysfunction
Previous rheumatic heart disease without valvular dysfunction
Pacemakers, defibrillators or stents

Infective Endocarditis Prophylaxis recommended[5,34,36]
Dental procedure: tooth extraction, periodontal surgery, brushing teeth, dental implant, root canal, gingival placement of bands, orthodontic treatment, intraligamentary injections, professional cleaning and scaling
Respiratory procedure: tonsillectomy or adenoidectomy, surgery that involve respiratory mucosa, rigid bronchoscopy
Gastrointestinal procedure: endoscopy, sclerotherapy for oesophageal varices, oesophageal dilatation, endoscopic retrograde cholangiography, gallbladder surgery, surgery that involve intestinal mucosa
Genitourinary procedure: prostatic surgery, cystoscopy, urethral dilatation

Prophylaxis regimens[5,37]
General profilaxis:
– Amoxicilin: 50 mg/kg orally 1 h before procedure
– Ampicillin: 50 mg/kg IM or IV 30 min before procedure

Allergic to penicillin:
– Clindamycin: 20 mg/kg orally 1 h before procedure
– Cephalexin or cefadroxil: 50 mg/kg orally 1 h before procedure
– Azithromycin or clarithromycin: 15 mg/kg orally 1 h before procedure
– Clindamycin: 20 mg/kg IV 30 min before procedure
– Cefazolin: 25 mg/kg IM or IV 30 min before procedure

Adapted from[4-6,34-38].

COMPLICATIONS AND OUTCOME

The clinical situations that favour complications[4,31,32] and surgical indications according to the anomalies found at echocardiography are listed in table 5. Coward et al[33] reported a 49% incidence of complications. Mylonakis et al[15] found 20-25% adult mortality secondary to endocarditis. Danilowicz[6] recorded a 20-30% incidence of mortality in paediatric age patients, but recently some authors[33] have determined the incidence to be 12%.

PREVENTION

The indications and doses of antibiotics to prevent infectious endocarditis are listed in table 6[4-6,34-38].

CONCLUSION

1. Paediatric infectious endocarditis is rare, but its incidence has risen owing to the survival of children with operated congenital heart disease.

2. In recent decades, the paediatric population at risk of endocarditis has changed, given the increase of children with immunodeficiency disease and children under neonatal and paediatric intensive care.

3. Infectious endocarditis in healthy children is rare but not exceptional.

4. Complications continue to be frequent.

5. Diagnostic criteria are guidelines that do not replace clinical judgement.

REFERENCES

1. Millar BC, Moore JE. Emerging issues in infective endocarditis. Emerging Infectious Diseases. 2004;10:1110-6. Available at: www.cdc.gov/eid

2. Contrepois A. Towards a history of infective endocarditis. Medical History. 1996;40:25-54.

3. Fye WB, Fernel JF. Profiles in Cardiology. Clin Cardiol. 1997;20: 1037-8.

4. Ferrieri P, Gewitz MH, Gerber MA, Newburger JW, Dajani AS, Shulman ST, et al. Unique features of infective endocarditis in childhood. Pediatrics. 2002;109:931-43.

5. Brook MM. Pediatric bacterial endocarditis. Treatment and prophylaxis. Pediatr Clin North Am. 1999;46:275-87.

6. Danilowicz D. Infective endocarditis. Pediatr Rev. 1995;16: 148-54.

7. Fisher MC. Changing risk factors for pediatric infective endocarditis. Curr Infect Dis Reports. 2001;3:333-6.

8. Millard DD, Shulman ST. The changing spectrum of neonatal endocarditis. Clin Perinatol. 1988;15:587-608.

9. Werner AS, Cobbs CG, Kaye D, Hook EW. Studies on the bacteriemia of bacterial endocarditis. JAMA. 1967;202:199-203.

10. Stock JH, Sahn DJ. Endocarditis in the pediatric population. Curr Treat Op Cardiovasc Med. 2000;2:481-8.

11. Martin JM, Neches WH, Wald ET. Infective endocarditis: 35 years of experience at a Children's Hospital. Clin Infect Dis. 1997; 24:669-75.

12. Baltimore RS. Infective endocarditis in children. Pediatr Infect Dis J. 1992;11:907-13.

13. Gutschik E. Microbiological recommendations for the diagnosis and follow-up of infective endocarditis. Clin Microbiol Infect. 1998;4:S10-6.

14. Milazzo AS, Li JS. Bacterial endocarditis in infants and children. Review. Pediatr Infect Dis J. 2001;20:799-801.

15. Mylonakis E, Calderwood SB. Infective endocarditis in adults. N Engl J Med. 2001;345:1318-30.

16. Shanson DC. Infections of the heart. In: Wright, editor. Microbiology and clinical practice. 2nd ed. Toronto, 1989. p. 413-27.

17. Martin RP, Meltzer RS, Chia BL, Stinson EB, Popp RL. Clinical utility of two-dimensional echocardiography in infective endocarditis. Am J Cardiol. 1980;46:379-85.

18. Humpl T, McCrindle BW, Smallhorn JF. The relative roles of transthoracic compared with transesophageal echocardiography in children with suspected infective endocarditis. J Am Coll Cardiol. 2003;41:2068-71.

19. Ayres NA, Miller-Hance W, Fyfe DA, Stevenson JG, Sahn DJ, Young LT, et al. Indications and guidelines for performance of Transesophageal echocardiography in the patient with pediatric acquired or congenital heart disease. J Am Soc Echocardiogr. 2005;18:91-8.

20. Aly AM, Simpson PM, Humes RA. The role of transthoracic echocardiography in the diagnosis of infective endocarditis in children. Arch Pediatr Adolesc Med. 1999;153:950-4.

21. Lukes AS, Bright DK, Durack DT. Diagnosis of infective endocarditis. Infect Dis Clin North Am. 1993;7:1-8.

22. Kadir IS, Barker TA, Clarke B, Denley H, Grötte GJ. Recurrent acute rheumatic fever: A forgotten diagnosis? Ann Thorac Surg. 2004;78:699-701.

23. Von Reyn CF, Levy BS, Arbeit RD, Friedland G, Crumpacker CS. Infective endocarditis: an analysis based on strict case definitions. Ann Intern Med. 1981;94:505-18.

24. Durack DT, Lukes AS, Bright DK. New Criteria for diagnosis of infective endocarditis: utilization of specific echocardiographic findings. Am J Med. 1994;96:200-9.

25. Li JS, Sexton DJ, Mick N, Nettles R, Fowler VG, Ryan T, et al. Proposed modifications to the Duke Criteria for the diagnosis of infective endocarditis. Clin Infect Dis. 2000;30:633-8.

26. Rognon R, Kehtari R. Individual value of each of the Duke Criteria for the diagnosis of infective endocarditis. Clin Microbiol Infect. 1999;5:396-403.

27. Stockheim JA, Chadwick EG, Kessler S, Amer M, Abdel-Haq N, Dajani AS, et al. Are the Duke criteria superior to the Beth Israel Criteria for the diagnosis of infective endocarditis in children? Clin Infect Dis. 1998;27:1451-6.

28. Marco del Pont J, De Dicco LT, Vartalitis C, Ithurralde M, Gallo JP, Vargas F, et al. Infective endocarditis in children: clinical analyzes and evaluation of two diagnostic criteria. Pediatr Infect Dis J. 1995;14:1079-86.

29. Tissières P, Gervaix A, Beghetti M, Jaeggi ET. Value and limitations of the von Reyn, Duke and modified Duke Criteria for the diagnosis of infective endocarditis in children. Pediatrics. 2003;112:e467-e71.

30. Millar BC, Moore JE. Current trends in the molecular diagnosis of infective endocarditis. Europ J Clin Microbiol & Infect Dis. 2004;23:353-65.

31. Bayer A, Bolger A, Taubert K, Wilson W, Steckelberg J, Karchmer AW, et al. Diagnosis and management of infective endocarditis and its complications. Circulation. 1998;98: 2936-48.

32. Devlin RK, Andrews MM, Von Reyn CF. Recent trends in infective endocarditis: Influence of case definitions. Curr Op Cardiol. 2004;19:134-9.

33. Coward K, Tucker N, Darville T. Infective endocarditis in Arkansan children from 1990 through 2002. Pediatr Infect Dis J. 2003;22:1048-52.

34. Horstkotte D and the Task Force on Infective Endocarditis of the European Society of Cardiology. Guidelines on Prevention, Diagnosis and treatment of infective endocarditis. Eur Heart J. 2004;25:267-76.

35. Oliver R, Roberts GJ, Hooper L. Penicillins for the prophylaxis of bacterial endocarditis in dentistry [Review]. The Cochrane Database Syst Rev 2004;(2):CD003813.

36. Durack DT. Prevention of infective endocarditis. N Engl J Med. 1995;332:38-44.

37. Dajani AS, Taubert KA, Wilson W, Bolger AF, Bayer A, Ferrieri P, et al. Prevention of bacterial endocarditis. Recommendations by the American Heart Association. JAMA. 1997;277: 1794-801.

38. Baddour LM, Wilson WR, Bayer AS, Fowler VG, Bolger AF, Levison ME. Infective endocarditis. Diagnosis, antimicrobial therapy and management of complications. Circulation. 2005; 111:e394-e434.