Endocarditis in the 21st Century

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I undersign, Monica Mariana Baluta, certificate that I do not have any financial or personal relationships that might bias the content of this work.

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ABSTRACT

Endocarditis still carries a poor prognosis despite improvement in preventive strategies and advances in diagnosis and also in treatment. Epidemiology of infective endocarditis (IE) has changed in late years. Contemporary antibiotic overuse determines antibiotic resistance against microorganisms involved in IE. Prophylaxis principles have been changed and restricted in order to avoid excessive antibiotic use and unfounded costs. Current guidelines are often based on expert opinion because of the low incidence of the disease, the absence of randomized trials, and the limited number of meta-analyses. The present review will focus on current changes in epidemiology, prophylaxis, diagnosis and treatment options.

Keywords: infective endocarditis, epidemiology, prophylaxis, treatment options

INTRODUCTION

Infective endocarditis (IE) is a syndrome that is permanently changing, with new high risk patients and new microorganisms, with more intracardiac device infections, with intravenous drug abusers, and increasing nosocomial infections.

Development of preventive strategies and diagnostic procedures and advances in treatment are not enough to improve the poor prognosis due to elevated mortality.

Current definition and classification

IE represents an infection of the endocardial surface of the heart, including large intrathoracic vessels and intracardiac foreign bodies, microorganisms being present in the characteristic lesion. IE is a syndrome rather than a disease, diagnosis being established on many findings.

The old term bacterial endocarditis has been replaced with the term infective endocarditis (1). Bacterial endocarditis was an inappro-

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priate term ignoring the nonbacterial forms of IE (2). Of historical relevance is also the classification in acute and subacute IE. The current terms and classification endorsed by ESC were updated in the last guideline and are exposed in Table 1 (3).

Epidemiological modification

The incidence of infective endocarditis varies between countries because the criteria for diagnosis and the methods of reporting vary with different series determining a lack of uniformity in registering the disease.

The reported incidence is 3-10 episodes/100,000 person/year (4,5). The mean age of patients with IE has gradually increased in the antibiotic era. The incidence of IE decreases in young patients in present days, but increased abruptly with age, with a peak incidence of 14.5 episodes/100,000 person/year between 70-80 years of age (3).

Many factors are related to this shift in age distribution: 1) the age of the population has been increasing steadily; 2) people with rheumatic or congenital heart disease are surviving longer 3) the underlying heart disease change etiology-elderly characteristic degenerative heart disease took place of rheumatic heart disease; 4) more frequent prosthetic valve surgery;

5) new at-risk groups has emerged, including intravenous drug users, patients with intracardiac devices, and those exposed to healthcare associated bacteriemia (e.g., intravenous catheters).

Male sex appears to be more frequent involved than female in all epidemiological studies, with a male: female ratio that can exceed 2:1 with a range of 1 to 3:1 in 18 large series. Despite increased male incidence, female are prone to an altered prognosis (6).

Current infectious etiology

Streptococci and staphylococci remain responsive for the majorities of cases with identified microbiology. Streptococci are common in NVE and late PVE, *Staphylococcus aureus* and Coagulase-negative staphylococci being dominant in early PVE, and tricuspid valve *S. aureus* infection in IV drug abusers (Table 2) (7).

Culture-negative endocarditis remain a problem and may be due to a number of factors: 1) cultures taken toward the end of a chronic course (>3 months), 2) slow growth of fastidious organisms (anaerobes, *Haemophilus* spp., *Actinobacillus* spp., *Cardiobacterium* spp., or *Brucella* spp.), 3) fungal IE; 4) IE caused by intracellular parasites (rickettsiae, chlamydiae, T. whippelii, possibly viruses), 5) uremia superve-

Based on fulfilling of current diagnosis criteria		Definite Suspected Possible
Related to anatomical site	Cardiac	Left-sided IE: - native valve endocarditis (NVE) - prosthetic valve endocarditis (PVE) 1. early PVE (<1 year after valve surgery) 2. late PVE (>1 year after valve surgery) Right-sided IE
	Device related IE	pacemaker, cardioverter/defibrilator
Acquisition mode	Community acquired	
	Health care associated:	Nosocomial/ Non-nosocomial
	Intravenous drug abuse-associated IE	
Related to recurrence	Relapse	another episode of IE caused by the same microorganism <6 month following first episode
	Reinfection	another episode of IE caused by the other microorganism >6 month following first episode
Related to disease activity	Active IE	persistent infection in blood and/or in pathogenic lesion, or patient under antibiotic therapy
	Healed IE	refer to cured IE
Based on the etiologic agent responsible	IE with positive blood cultures IE with negative blood cultures because of prior antibiotic treatment IE frequently associated with negative blood cultures IE associated with constantly negative blood cultures	

TABLE 1. Classification and definitions of infective endocarditis

Adapted from reference (3)

ning in a chronic course; 6) mural thrombi IE, as in post–myocardial infarction, or infection related to pacemaker wires, 7) noninfective Libman-Sacks endocarditis or, 8) an incorrect diagnosis.

A proper collection of blood culture specimens together with care in the performance of serologic tests, and use of newer diagnostic techniques may reduce the proportion of culture-negative cases (8). ❑

DIAGNOSIS

Since Osler's clinical diagnosis based on the classical signs, infective endocarditis diagnosis has improved today by using microbiological tests and echocardiography (10).

1) Clinical diagnosis

Clinical features (Table 3) may present as an acute, rapidly progressive infection, but the disease usually runs a subacute evolution with multiple nonspecifics, confusing symptoms.

2) Microbiological diagnosis

Identifying the offender microorganism is one of the most important tests for diagnosis of IE at this time and can be done using: (1) the culture of viable microorganisms from the blood or from cardiac tissue; (2) phenotypic identification of the isolates after the culture results; (3) molecular identification methods: nucleic acid target, signal amplification, and/or sequence analysis that give a specific and fast alternative to the previous methods. Molecular methods provide now the best tools for detection in those cases where the culture of responsible microorganism is difficult or impossible to obtain in case of fastidious germs and prior antimicrobial treatment. PCR (polymerase chain reaction) permit a rapid and reliable recognition of fastidious and non-culturable agents (8, 11,12).

A minimum of 3 blood culture sets (no more than two bottles per venipuncture) must be obtained in the first 24 hours of admission (3). At least 2 separate sets of blood cultures taken 30 min apart by separate venipunctures should be obtained within the first 1-2 hours of presentation. Positive blood culture represents a major criteria for IE diagnosis and it is defined as the following:

- 2 separate positive blood cultures (BC), in the absence of a primary focus, with typical microorganisms related to IE (Vi-

Agent	Endocarditis all type (%)	Early PVE <12 months (%)	Late PVE > 12 months (%)
Streptococci	60–80 (30–40 Viridans)	2	28
Staphylococci	20–35	25 (S Aureus)	17 (S Aureus)
Coagulase-positive	10–27	25 (S Aureus)	17 (S Aureus)
Coagulase-negative	1–3	29	12
Enterococci	5–18	10	14
Gram-negative aerobic bacilli	1.5–13	13	5
Fungi	2–4	7	2
Culture-negative	<5–24	8	9
Polymicrobial	Rare	2	5
Diphtheroids	NA	3	2
Coxiella burnetii	NA	-	2

TABLE 2. Etiologic agents in infective endocarditis

PVE - prosthetic valve endocarditis.
Adapted from references (2,9)

Symptoms	Patients (%)	Signs	Patients (%)
Fever	80	Fever	90
Chills	40	Heart murmur	85
Weakness	40	Changing murmur	5–10
Dyspnea	40	New murmur	3–5
Weight loss	25	Embolic phenomenon	>50
Cough	25	Skin manifestations	18–50
Skin lesions	20	Osler nodes	10–23
Stroke	20	Splinter hemorrhages	15
Nausea/vomiting	20	Petechiae	20–40
Headache	20	Janeway lesion	<10
Myalgia/arthralgia	15	Splenomegaly	20–57
Delirium/coma	10–15	Septic complications	20
Hemoptysis	10	Mycotic aneurysms	20

TABLE 3. Clinical manifestations of infective endocarditis

ridans streptococci, Streptococcus bovis, HACEK group, *Staphylococcus aureus*; community-acquired enterococci) (3)

- persistently positive BC with microorganisms consistent with IE defined as: 1) at least 2 positive cultures of blood samples drawn >12 h apart; or 2) all 3 or a majority of ≥ 4 separate BC (with first and last sample drawn at least 1 h apart) (3)
- single positive BC for Coxiella burnetii or antiphase I IgG antibody titer >1:800 (3)

3) Echocardiography

Transthoracic and transoesophageal echocardiography (TTE/TEE) identify de characteristics lesion: the vegetation, abscesses, pseudoaneurysm, perforation, fistula, valve aneurysm, and dehiscence of a prosthetic heart valve (13, 14).

The sensitivity of TTE is acceptable (40 to 63%) and that of TEE is very good (90 to 100%) (15). According to new European guideline, echocardiography is recommended: for diagnostic purposes and follow-up of the therapy, intra-operatively, and following completion of therapy (3,16).

Transthoracic echocardiography

TTE is the first line imaging tool for diagnosis in suspected IE. If TTE is initially negative and IE suspicion persists, it can be repeated at 7-10 days. If good quality negative TTE is obtained in case of low suspicion, no TEE is indicated. TTE should be used for follow up of the medi-

cally treated patient with suspected complication (class I- ESC recommendation) or without suspected complication (class IIa -ESC) as well as for evaluation of cardiac and valve morphology and function at completion of antibiotic therapy.

Transoesophageal echocardiography

TEE is recommended for diagnosis in high suspicion cases with negative TTE, can be repeated at 7-10 days if initially negative and high IE suspicion persist, and is not indicated when TTE is frankly negative in low suspicion patient (class III-ESC). Expert's opinion is that TEE should be used in the majority of patients with suspected IE (class IIa- ESC). For the follow up of medically treated patient TEE have same indication as TTE.

Echocardiography provides the evidence for endocardial involvement, the other major criteria in current revised diagnosis criteria (3, 17,18).

4) Criteria for diagnosis

Longtime used Duke criteria of IE were revised over the time and amended by some of Li recommendation and are exposed simplified in Table 4 (3,17,18). Those criteria used in previous epidemiological studies have a high sensitivity and specificity for the diagnosis but they do not replace clinical judgment, especially in the setting of new forms of IE. ❑

Definite IE	Possible IE	Rejected IE
Clinical criteria		Alternate diagnosis
2 Major criteria or	1 major and 1 minor criteria	Resolution of the infection with
1 major and 3 minor criteria	Or	antibiotic treatment for <4 days
Or 5 minor criteria	3 minor criteria	No histological evidence
Definition of terms		
Major criteria		
1. Positive blood cultures		
2. Evidence of endocardial involvement (TTE/TEE; histological specimen)		
3. New valvular regurgitation (clinical modification of pre-existing murmur not enough)		
Minor criteria		
1. Predisposition (previous IE, predisposing heart condition, injection drug use)		
2. Fever, temperature >38 ° C		
3. Vascular phenomena		
4. Immunologic phenomena		
5. Microbiological evidence: positive BC that not met major criteria characteristics		
Echocardiographic minor criteria eliminated		
"St Thomas" minor criteria, proposed by Lamas & Eykyn, not added but helpful in judgement: CRP > 100 mg/l, ESR elevation, splenomegaly, haematuria, clubbing, splinter haemorrhagia, petechiae and purpura, central non-feeding venous lines, peripheral venous lines (18)		

TABLE 4. Diagnostic criteria for infective endocarditis (IE)

Adapted from references (2,3,17,18)

TREATMENT

The treatment of endocarditis represents a major triumph of "modern medicine" and a continuing challenge. Antibiotic and surgical therapies together with complication management are now the keystone of disease management.

1) Antimicrobial therapy

Effective antimicrobial therapies consist first in identification of the specific pathogen and assessment of its susceptibility to antimicrobial agents.

Minimal requirements for an effective antimicrobial regimen include the following: bactericidal activity; high concentrations of the antimicrobial agent in the vegetation; prolonged duration of antimicrobial therapy; dosing should be frequent enough to prevent the growth of microorganisms between doses.

In severely ill patients at risk of death, empirical antibiotic therapy should be started promptly after a classic minimum of three sets of blood cultures at 30 min interval are drawn (19).

Associations between different classes are developed and studied over the time in order to cover a wide spectrum of isolates. Antimicrobial activity should be evaluated properly and toxic effects of drugs should be evaluated sequentially (20).

Treatment must be adjusted immediately after identification of the pathogen. Proposed ESC empirical treatment for patients with IE is exposed in Table 5.

Outpatient parenteral antibiotic therapy (OPAT) for infective endocarditis is a concept that emerged in the past years and has today a quite well applicability with >250,000 patients/year reported in the USA and it is used to consolidate antimicrobial therapy (21). The following reasons may be responsible for OPAT expansion: established safety, hospitals cost savings, new antibiotics that permit a longer spacing of doses, new diagnostic and reliable monitoring technology, interested and trained medical professionals, patient preference and benefits, prompt return to work. Risks of OPAT are treatment failure or complications (line problems, thrombosis, and anaphylaxis). Patient-Selection Criteria are the following: medically stable patient (established control of infection-related complications), after 2 weeks of hospital therapy. Exceptionally OPAT is accepted for the first phase of treatment if the patient remains stable, without complication and with IE due to oral streptococci etiology, otherwise OPAT it is not recommended in the first phase. After discharge the patient should be monitored daily by a nurse and once or twice per week by responsible doctor (22).

2) Surgical therapy

Surgery can be required in up to 50% of IE cases in which the cure with antibiotic treatment appear improbable (7). The main indications for surgery are the following:

1) heart failure with hemodynamic instability which remain refractory to the medical treatment

2) uncontrolled infection with complication

3) prevention of systemic embolism in patient with large or very large vegetation with an embolic event or other predictors of a compli-

		Dose, route, duration	
NVE & Late PVE	Ampicillin Sulbactam (Amoxicillin Clavulanate) plus	12 g/ day iv in 4 doses	4 - 6 W
	Gentamicine Or	3 mg/kg/day in 2- 3 doses iv/im	4 -6 W
	Vancomycin Plus	30 mg/ kg/day in 2 doses IV	4 - 6 W
	Gentamicin Plus	3 mg/kg/day in 2-3 doses iv/im	4 - 6 W
	Ciprofloxacin	1000 mg/day in 2 doses orally Or 800 mg/day in 2 doses iv	4 - 6 W
Early PVE	Vancomycin Plus	30 mg/ kg/day in 2 doses IV	6 W
	Gentamicin Plus	3 mg/kg/day in 2-3 doses iv/im	2 W
	Rifampin	1200 mg/day in 2 doses orally	

TABLE 5. ESC suggested recommendation for empirical antibiotic therapy in endocarditis

NVE - native valve endocarditis; PVE - prosthetic valve endocarditis, W- weeks
Adapted from reference (3)

cated course despite appropriate antimicrobial treatment

The timing of surgery, early or late in evolution, is still controversial, with advantages and disadvantages for both (Table 6) (23,24). Early valve surgery appears beneficial in terms of long-term survival and improved prognosis, but is correlated with increased early postoperative mortality (25).

IE mortality in surgical intervention for removal of infected tissues and reconstruction of cardiac morphology vary from 5 to15% and is related to microbial etiology, the extent of damage of cardiac structures, the left ventricular dysfunction, and the patient's hemodynamic status at the time of surgery (3).

It is of greatest importance that cardiologists, microbiologists and cardiac surgeons cooperate closely if IE occurs; especially if prosthetic valve endocarditis is suspected or definite. Other complications management of infective endocarditis is not the purpose of this paper.

New Principle of IE Prophylaxis

The hypotheses of bacteriemia prevention and/or minimization have determined the longtime use of antibiotics for endocarditis prophylaxis in patients with predisposing cardiac conditions prior specific procedures. Decisions were based primarily on observational studies and expert opinion.

Today many concerns appear related to antibiotic resistance against microorganisms involved in IE triggered by antibiotic overuse. There is no convincing evidence that antibiotic prophylaxis for every predisposing cardiac lesion was cost-effective (26).

In the past years, working groups of the American Heart Association (27,28) and the European Society of Cardiology (3) have revised their guidelines and has limited also EI prophylaxis to the highest risk patients (Table 7) undergoing the highest risk procedures (Table 8). ESC recommended prophylaxis consist of amoxicillin or ampicillin, single dose 30-60 minutes before procedures, 2 g po or iv, or in case of allergy clindamycin 600 mg po or iv, same timing.

Current opinion is that the prevention should begin first with general measures such: surgical correction of congenital heart defects, maintaining good oral hygiene, dental prob-

Emergency Surgery (within 24 h)
- IE with refractory pulmonary edema or cardiogenic shock determined by
• Acute severe valvular regurgitation (aortic or mitral) or severe prosthetic dysfunction (dehiscence or obstruction)
• Fistula into a cardiac chamber or the pericardial space
Urgent Surgery (within days)
- IE with persistent heart failure, signs of hemodynamic instability on echocardiography determined by acute severe valvular (aortic or mitral) regurgitation or obstruction
- Uncontrolled infection (large vegetation, abscess, pseudoaneurism, fistulae)
- Fever and positive blood cultures persistence >7–10 days
- Large mitral or aortic vegetation (>10 mm) with an embolic event despite suitable antimicrobial treatment or other predictors of a complicated course(heart failure, persistent infection, abscess)
- Very large vegetation (>15 mm)
Early Elective Surgery (during the in-hospital stay)
- Severe aortic or mitral regurgitation with no heart failure
- Fungal or multiresistant infection infections resistant to medical therapy

TABLE 6. Timing of surgery in infective endocarditis

Adapted from reference (3,24)

1. Prosthetic cardiac valve
2. Previous IE
3. Selected congenital heart disease
• Nonrepaired cyanotic congenital heart disease, including palliative shunts and conduits
• Repaired (surgically/by catheter intervention) congenital heart defect with prosthetic material or device during the first 6 months after the procedure (until endothelialization occurs)
• Repaired congenital heart disease with residual defects at the side or adjacent to the site of a prosthetic patch or device

TABLE 7. The highest risk patients for infective endocarditis

* only AHA recommend EI prophylaxis for Cardiac transplantation recipients who develop cardiac valvulopathy
Adapted from (3,28)

Both guideline
Dental procedures that involve manipulation of gingival tissues or periapical region of teeth, or perforation of oral mucosa
AHA guideline only
Procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissues only if they imply overt incision of the skin or mucosa (ESC guideline recommend prophylaxis when a proven infection of those structures require specific intervention)

TABLE 8. The highest risk procedures for infective endocarditis

Adapted from (3,28)

lems ended before prosthetic valves implant, avoiding procedures that determine bacteriemia, minimizing the use of central intravascular catheters and urinary catheters and promptly treating any infection. ❑

CONCLUSION

If untreated, IE remains a fatal disease. Unfortunately lots of guidelines are often based on expert opinion because of the low incidence of the disease, the absence of randomized trials, and the limited number of meta-analyses (29). Successful management depends on the close cooperation of medical and surgical disciplines. This collaboration has markedly improved the outcome of the disease. ❑

ABREVIATIONS

AHA American Heart Association
BC blood cultures
CRP C reactive protein
ESC European Society of Cardiology
ESR erythrocyte sedimentation rate
IE Infective endocarditis
IIa ESC expert opinion recommendation of ESC
III ESC contraindication
Im intramuscular
IV intravenous
NVE native valve endocarditis
OPAT Outpatient parenteral antibiotic therapy
PCR polymerase chain reaction
PVE prosthetic valve endocarditis
TEE Transoesophageal echocardiography
TTE Transthoracic echocardiography

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