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# Native and Prosthetic Aortic Valve Endocarditis

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## 1. Introduction

### 1.1 Definitions

Infective endocarditis (IE) is an endovascular, microbial infection of intracardiac structures facing the blood, including infections of the large intrathoracic vessels and of intracardiac foreign bodies. The early characteristic lesion is a variably sized vegetation, although destruction, ulceration, or abscess formation may be seen earlier by echocardiography (Habib et al, 2009).

Prosthetic valve endocarditis (PVE) is classified as early or late, depending on when infection is diagnosed: early PVE (within 12 months after surgery) and late PVE (12 months or more after surgery).

Nosocomial IE is defined as an infection occurring > 72 h after admission to the hospital or IE acquired in association with a significant invasive procedure performed during a recent hospitalization ≤ 8 weeks before the onset of symptoms.

Persistent infection is defined as a repeat episode of IE caused by the same microorganism developing < 1 year after the first episode (Hill et al, 2007).

### 1.2 Historical perspective

The hypothesis of the role of parasites (microorganisms) microscopically observed in vegetations and in the cardiac valves of patients with endocarditis was first put forth by Winge in Sweden in 1869. Winge's work led Klebs and Rosenbach in Germany to establish, between 1878 and 1881, an animal model of experimental endocarditis in which the aortic valves of rabbits were perforated with a metallic probe (loaded with septic material) introduced through the carotid artery. Ten years after Winge's work, Pasteur emphasized the importance of bacteriologic "blood cultures". During the period 1881-1886, Netter and Grancher (Pasteur's associates) introduced a method for drawing aseptic blood samples from patients with clinical endocarditis and doing bacteriologic blood cultures. In Vienna in 1885-1886, Orth, Weichselbaum, and Wyssokowitsch further developed Rosenbach's procedure of inducing experimental endocarditis by injecting material from a bacterial culture into a rabbit's ear vein. The development of an experimental model of endocarditis by investigators in the latter part of the nineteenth century provided anatomopathological and bacteriologic data that in turn led to a better understanding of IE (Contrepois, 1995).

### 1.3 Epidemiology

The epidemiological profile of IE has changed substantially over the last few years. In industrialized countries, the typical pattern of IE is now an elderly patient with a degenerative heart valve disease or with a prosthetic valve or an intracardiac device such as a pacemaker or defibrillator leads. Major changes have occurred in the mode of acquisition of IE and in its microbiological profile (Thuny et al, 2010). Significant geographical variations have been shown. The highest increase in the rate of staphylococcal IE has been reported in the USA, where chronic hemodialysis, diabetes mellitus, and intravascular devices are the three major factors associated with the development of *Staphylococcus aureus* (*S. aureus*) endocarditis. In other countries, the main predisposing factor for *S. aureus* IE may be intravenous drug abuse (Habib et al, 2009).

### 1.4 Incidence

The incidence of IE ranges from one country to another within 3–10 episodes/100,000 person-years. This may reflect methodological differences between surveys rather than true variation. Of note, in these surveys, the incidence of IE was very low in young patients but increased dramatically with age—the peak incidence was 14.5 episodes/100,000 person-years in patients between 70 and 80 years old.

In all epidemiological studies of IE, the male:female ratio is 2:1, although why there is a higher proportion of men is poorly understood. Furthermore, female patients may have a worse prognosis and undergo valve surgery less frequently than their male counterparts (Habib et al, 2009).

Patients with prosthetic aortic valves are reported to have an incidence of PVE of 0.3 to 1.2 episodes per 100 patients/year, and approximately 1.4% of patients undergoing aortic valve replacement develop PVE during the first postoperative year.

### 1.5 Types of infective endocarditis

IE should be regarded as a set of clinical situations that are sometimes very different from each other. In an attempt to avoid overlap, the following four categories of IE must be separated according to the site of infection and the presence or absence of intracardiac foreign material: left-sided native valve IE, left-sided prosthetic valve IE, right-sided IE, and device-related IE (the latter includes IE developing on pacemaker or defibrillator leads with or without associated valve involvement).

With regard to acquisition, the following situations can be identified: community-acquired IE, healthcare-associated IE (nosocomial and non-nosocomial), and IE in intravenous drug abusers (IVDAs) (Habib et al, 2009).

### 1.6 Microbiology

The microbiology of IE of the aortic valve depends on whether the valve is native or prosthetic, and whether the infection is hospital- or community-acquired.

According to microbiological findings, the following categories are proposed:

1. IE with positive blood cultures.
   This is the most important category, representing 85% of all IE. Causative microorganisms are most often staphylococci, streptococci, and enterococci (Murdoch et al, 2009).
   a. IE due to streptococci and enterococci.
      Oral (formerly *viridans*) streptococci form a mixed group of microorganisms, which includes species such as *S. sanguis, S. mitis, S. salivarius, S. mutans,* and *Gemella*

*morbillorum*. Microorganisms of this group are almost always susceptible to penicillin. Members of the *S. milleri* or *S. anginosus* group (*S. anginosus, S. intermedius,* and *S. constellatus*) must be distinguished since they tend to form abscesses and cause hematogenously disseminated infections, that often require a longer duration of antibiotic treatment. Likewise, nutritionally variant "defective" streptococci, recently reclassified into other species (*Abiotrophia* and *Granulicatella*), should also be distinguished since they are often tolerant to penicillin [minimal bactericidal concentration (MBC) much higher than the minimal inhibitory concentration (MIC)]. Group D streptococci form the *Streptococcus bovis/ Streptococcus equinus* complex, including commensal species of the human intestinal tract, and were until recently gathered under the name of *Streptococcus bovis*. They, like oral streptococci, are usually sensitive to penicillin. Among enterococci, *E. faecalis, E. faecium*, and, to a lesser extent, *E. durans*, are the three species that cause IE.

b. Staphylococcal IE.
Traditionally, native valve staphylococcal IE is due to *S. aureus*, which is most often susceptible to oxacillin, at least in community-acquired IE. In contrast, staphylococcal prosthetic valve IE is more frequently due to coagulase-negative staphylococci (CNS) with oxacillin resistance. However, in a recent study of 1779 cases of IE collected prospectively in 16 countries, *S. aureus* was the most frequent cause, not only of IE, but also of prosthetic valve IE (Fowler et al, 2005). Conversely, CNS can also cause native valve IE (Chu et al, 2004, 2008) especially *S. lugdunensis*, which frequently has an aggressive clinical course.

2. IE with negative blood cultures because of prior antibiotic treatment.
This situation arises in patients who received antibiotics for unexplained fever before any blood cultures were done and in whom the diagnosis of IE was not considered; usually the diagnosis is eventually considered in the face of relapsing febrile episodes following antibiotic discontinuation. Blood cultures may remain negative for many days after antibiotic cesation, and causative organisms are most often oral streptococci or CNS.
3. IE frequently associated with negative blood cultures.
They are usually due to fastidious organisms such as nutritionally variant streptococci, fastidious Gram-negative bacilli of the HACEK group (*H. parainfluenzae, H. aphrophilus, H. paraphrophilus, H. influenzae, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella corrodens, Kingella kingae,* and *K. denitrificans*), *Brucella*, and fungi.
4. IE associated with constantly negative blood cultures.
They are caused by intracellular bacteria such as *Coxiella burnetii*, *Bartonella*, *Chlamydia*, and, as recently demonstrated, *Tropheryma whipplei*, the agent of Whipple's disease (Richardson et al, 2003). Overall, these account for up to 5% of all IE. Diagnosis in such cases relies on serological testing, cell culture, or gene amplification (Habib et al, 2009).

### 1.7 Pathophysiology

Healthy valve endothelium is resistant to colonization and infection by circulating bacteria. However, mechanical disruption of the endothelium results in the exposure of underlying extracellular matrix proteins, the production of tissue factor, and the deposition of fibrin and platelets as a normal healing process. Such nonbacterial thrombotic endocarditis (NBTE) facilitates bacterial adherence and infection (Prendergast, 2006).

Endothelial damage may result from mechanical lesions induced by turbulent blood flow, electrodes or catheters, inflammation, as in rheumatic carditis, or, in the elderly, degenerative changes associated with inflammation, micro-ulcers, and microthrombi.
Endothelial inflammation without valve lesions may also promote IE. Local inflammation triggers endothelial cells to express integrins of the b1 family (very late antigen). Integrins are transmembrane proteins that can connect extracellular determinants to the cellular cytoskeleton. Integrins of the b1 family bind circulating fibronectin to the endothelial surface while *S. aureus* and some other IE pathogens carry fibronectin-binding proteins on their surface. Hence, when activated endothelial cells bind fibronectin, they provide an adhesive surface for circulating staphylococci. Once adherent, *S. aureus* trigger their active internalization into valve endothelial cells, where they can either persist and escape host defenses and antibiotics, or multiply and spread to distant organs. Thus, there are at least two scenarios for primary valve infection: one involving a physically damaged endothelium, favoring infection by most types of organism, and one occurring on physically undamaged endothelium, promoting IE due to *S. aureus* and other potential intracellular pathogens.
The role of bacteremia has been studied in animals with catheter-induced NBTE. Both the magnitude of bacteremia and the ability of the pathogen to attach to damaged valves are important. Of note, bacteremia does not occur only after invasive procedures, but also as a consequence of chewing and tooth brushing. Such spontaneous bacteremia is low-grade and of short duration.
Classical IE pathogens (*S. aureus*, *Streptococcus spp.*, and *Enterococcus spp.*) share the ability to adhere to damaged valves, trigger local procoagulant activity, and nurture infected vegetations in which they can survive. They are equipped with numerous surface determinants that mediate adherence to host matrix molecules present on damaged valves (e.g. fibrinogen, fibronectin, platelet proteins) and trigger platelet activation. Following colonization, adherent bacteria must escape host defenses.
Gram-positive bacteria are resistant to complement. However, they may be the target of platelet microbicidal proteins (PMPs), which are produced by activated platelets and kill microbes by disturbing their plasma membrane. Bacteria recovered from patients with IE are consistently resistant to PMP-induced killing, whereas similar bacteria recovered from patients with other types of infection are susceptible. Thus, escaping PMP-induced killing is a typical characteristic of IE-causing pathogens (Habib et al, 2009).

## 2. Diagnosis

The diagnosis of IE remains a continuous challenge. It must be suspected in the presence of a new regurgitant heart murmur, embolic events of unknown origin, sepsis of unknown cause, and fever. IE should be suspected if fever is associated with intracardiac prosthetic material, a previous history of IE, previous valvular or congenital heart disease, and other predisposition or conditions for IE (immunocompromised state, evidence of congestive heart failure, conduction disturbance, vascular or immunologic phenomena, unexplained focal or non-specific neurological symptoms and signs, etc.). Echocardiography (transthoracic, transesophageal) and microbiological diagnosis confirm the diagnosis.
When diagnosing IE, molecular biology techniques such as PCR are rapid and reliably detect fastidious and nonculturable agents in patients, but they have inherent limitations, such as they cannot be reliably applied to whole blood samples, they risk contamination,

they yield false-negatives because of PCR inhibitors in clinical samples, they are unable to provide information about bacterial sensitivity to antimicrobial agents, and they are persistently positive despite clinical remission.

The variability in the clinical presentation of IE requires a diagnostic strategy that is both sensitive for disease detection and specific for its exclusion across all forms of the disease. In 1994, a diagnostic schema, termed the Duke criteria, was proposed. It stratified patients with suspected IE into 3 categories: "definite" cases, identified either clinically or pathologically (IE proved at surgery or autopsy); "possible" cases (not meeting the criteria for definite IE); and "rejected" cases (no pathological evidence of IE at autopsy or surgery, rapid resolution of the clinical syndrome with either no treatment or short-term antibiotic therapy, or a firm alternative diagnosis) (Durack et al, 1994; Baddour et al, 2005).

The revised Duke Clinical Diagnostic Criteria for IE were published in 2000, and included the following changes: the category "possible IE" was defined as having at least 1 major criterion and 1 minor criterion or 3 minor criteria; the minor criterion "echocardiogram consistent with IE but not meeting major criterion" was eliminated, given the widespread use of transesophageal echocardiography (TEE); bacteremia because of *S. aureus* was considered a major criterion, regardless of whether the infection was nosocomially acquired or whether a removable source of infection was present; and positive Q-fever serology was changed to a major criterion (Li et al, 2000).

| |
|---|
| **Major Criteria** |
| Two positive blood cultures for organisms typical of endocarditis |
| Three positive blood cultures for organisms consistent with endocarditis |
| Serologic evidence of *Coxiella burnetii* |
| Echocardiographic evidence of endocardial involvement: oscillating intracardiac mass on a heart valve, on supporting structures, in the path of regurgitant jets, or on implanted material without another anatomic explanation, cardiac abscess, new dehiscence of prosthetic valve, new valvular regurgitation |
| **Minor Criteria** |
| Predisposing heart disorder, intravenous drug abuse, fever ≥ 38°C |
| Vascular phenomena: arterial embolism, septic pulmonary embolism, mycotic aneurysm, intracranial hemorrhage, conjunctival petechiae, Janeway lesions |
| Immunologic phenomena: glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor |
| Microbiologic evidence of infection consistent with but not meeting major criteria |
| Serologic evidence of infection with organisms consistent with endocarditis |
| For definite clinical diagnosis: 2 major criteria or 1 major criterion and 3 minor criteria or 5 minor criteria |
| For possible clinical diagnosis: 1 major criterion and 1 minor criterion or 3 minor criteria. |
| For rejection of diagnosis: Firm alternative diagnosis explaining the findings of IE, resolution of symptoms and signs after antimicrobial therapy for ≤ 4 days, no pathologic evidence of infective endocarditis found during surgery or autopsy, or failure to meet the clinical criteria for possible endocarditis |

Table 1. Revised Duke Clinical Diagnostic Criteria for IE (Adapted from Li et al, 2000)

### 2.1 Clinical features

Symptoms and signs of IE are nonspecific: fever (94%), malaise (81%), fatigue (66%), loss of appetite (52%), dyspnoea (50%), cough (45%), sweating (37%), chills (37%), weight loss (35%), myalgia/arthralgia (25%), back pain (9%), vascular phenomena (53%), and splenomegaly (31%). Cardiac symptoms or signs (that is, new or altered cardiac murmur, heart failure) are recorded in half of the patients. In 36% of the episodes, neurological signs are present. They are more common in patients over 55 years old. Intracranial hemorrhages occur in 2%. Splenomegaly is found less often in patients over 55 years old than in younger patients. Most patients developed hematuria (79%) or anaemia (91%). Patients with anemia are more prone to malaise and loss of appetite. Anaemia occurs more often in patients with vegetations (Netzer et al, 2000).

### 2.2 Microbiological diagnosis

#### 2.2.1 Blood cultures

Positive blood cultures remain the cornerstones of diagnosis and provide live bacteria for susceptibility testing. Three sets (including at least one aerobic and one anaerobic), each containing 10 ml of blood obtained from a peripheral vein using a meticulously sterile technique, is virtually always sufficient to identify the usual microorganisms—the diagnostic yield of repeated sampling thereafter is low. Sampling from central venous catheters should be avoided in view of the high risk of contaminants (false-positives, typically staphylococcal) and misleading findings (Habib et al, 2009). Although infective endocarditis secondary to anaerobic infection is uncommon, cultures should be sent for both aerobic and anaerobic incubation. No evidence suggests that cultures should be taken coincident with peaks of temperature, as bacteremia is constant (Beynon et al, 2006).

#### 2.2.2 Culture-negative infective endocarditis and atypical organisms

Blood-culture negative IE (BCNIE) occurs in 2.5-31% of all cases of IE, often delaying diagnosis and the initiation of treatment, with profound impact on clinical outcome. BCNIE arises most commonly as a consequence of prior antibiotic administration, underlying the need for withdrawing antibiotics and repeating blood cultures in this situation. An increasingly common scenario is infection by fastidious organisms (including *Legionella*, *Coxiella*, the HACEK group and fungi such as *Candida*, *Histoplasma*, and *Aspergillus* species) with limited proliferation under conventional culture conditions, or requiring specialized tools for identification. These organisms may be particularly common in IE and affect patients with prosthetic valves, indwelling venous lines, pacemakers, renal failure, and immunocompromised states.

#### 2.2.3 Histological/immunological techniques

Pathological examination of resected valvular tissue or embolic fragments remains the gold standard for diagnosing IE and may also guide antimicrobial treatment if the causative agent can be identified using special stains or immunohistological techniques. Electron microscopy is highly sensitive and may help characterize new microorganisms, but it is time consuming and expensive. *Coxiella burnetii* and *Bartonella* species may be easily detected using serological testing with indirect immunofluorescence or an enzyme-linked immunosorbent assay (ELISA), and recent data (Watkin et al, 2006) demonstrate similar utility for staphylococci. An immunological analysis of urine may allow the detection of

microorganism degradation products, and ELISA detection of *Legionella* species has been described (Helbig et al, 2001). Incorporating these methods into accepted diagnostic criteria awaits prospective validation.

#### 2.2.4 Molecular biology techniques

The polymerase chain reaction (PCR) allows rapid and reliable detection of fastidious and nonculturable agents in patients with IE.

PCR uses nucleic acid target or signal amplification, alone or in combination with sequence analysis. The technique is particularly useful when negative cultures are caused by previous administration of antibiotics (as the technique is culture independent) or the presence of a fastidious organism and to identify the culprit organism in polymicrobial infection (Beynon et al, 2006).

### 2.3 Echocardiography

Echocardiography plays a key role in IE, concerning its diagnosis, the diagnosis of its complications, its follow-up under therapy and prognostic assessment. Echocardiography is particularly useful for the initial assessment of embolic risk and in decision-making in IE.

Transesophageal echocardiography (TEE) plays a major role both before surgery and during surgery (intraoperative echocardiography).

Echocardiographic results must be taken into consideration for both the decision to operate or not and the choice of the optimal timing for surgery. In all cases, however, the results of echocardiographic studies may be interpreted taking into account the clinical features of the patient (Habib et al, 2010).

#### 2.3.1 Transthoracic echocardiography

Transthoracic echocardiography (TTE) is the initial technique of choice for investigating IE. In low-risk patients, a normal transthoracic echocardiogram provides confirmation that endocarditis is unlikely and suggests that investigations should be directed elsewhere (Beynon et al, 2006). If the clinical suspicion is high, TEE should be used.

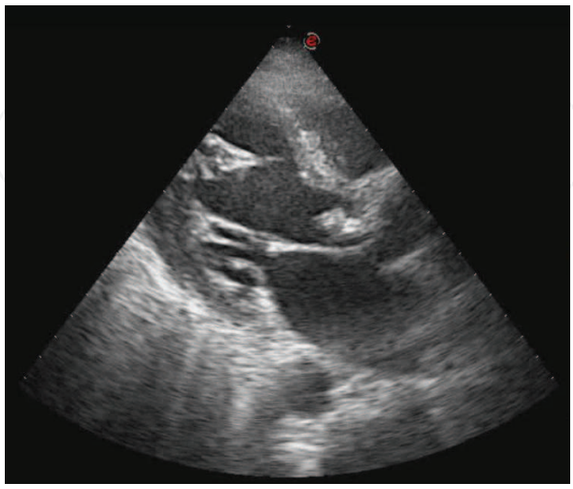


Fig. 1. Parasternal long axis view from TTE of a native aortic valve vegetation with aortic valve rupture

The sensitivity of TTE ranges from 40% to 63%. There is no better technique for noninvasive visualization of vegetations than echocardiography. Overall, the TTE detection rate for vegetations in patients with a clinical suspicion of endocarditis averages around 50%. The diagnostic yield of the technique in detecting vegetations is influenced by several factors: image quality; echogenicity and vegetation size; vegetation location; presence of previous valvular disease or valvular prosthesis; experience and skill of the examiner; and pretest probability of endocarditis (Evangelista & Gonzalez-Alujas, 2004).

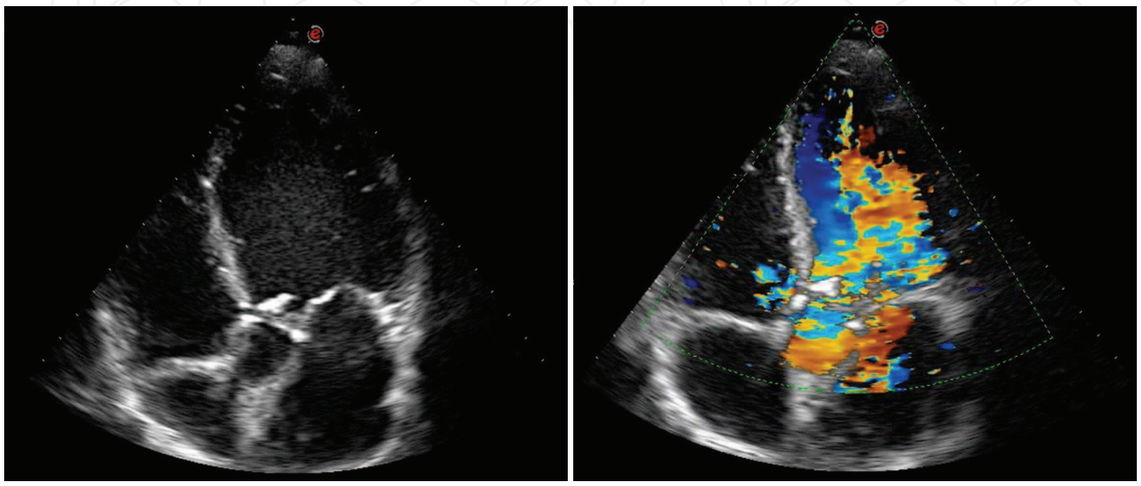


Fig. 2. Native aortic valve vegetation (left TTE and right color Doppler ultrasound)

### 2.3.2 Transesophageal echocardiography

In most cases, TTE is sufficient. TEE is indicated when mechanical prosthetic valves are present, to detect right-sided lesions and to visualize myocardial abscesses. TEE may be considered an invasive procedure, but it is only modestly uncomfortable to the patient, can be rapidly done, and is low-risk. It is more sensitive than conventional TTE for detecting valvular vegetations. Furthermore, it may detect an unsuspected paravalvular abscess, and it correlates well with surgical and pathologic findings. The sensitivity of TEE ranges from 90% to 100%.

In high-risk groups, TEE, with its higher sensitivity and specificity, may be needed if the TTE is normal and suspicion of IE remains high. TEE is also used to investigate potential complications of IE (Beynon et al, 2006). TEE is particularly useful in patients with prosthetic valves and for evaluating myocardial invasion. Negative TEE has a negative predictive value of over 92% for IE (Mylonakis & Calderwood, 2001).

## 2.4 Other imaging technologies

Other advances in imaging technology have had minimal impact in routine clinical practice. Using harmonic imaging has improved study quality, while three-dimensional echocardiography and other alternative modes of imaging— computed tomography (CT), magnetic resonance imaging (MRI), positron emission tomography (PET), and radionuclide scanning— have yet to be evaluated in IE. Multislice CT has recently been shown to give better results than does TEE when evaluating IE-associated valvular abnormalities, particularly when assessing the perivalvular extent of abscesses and pseudoaneurysms (Habib et al, 2009).

### 2.5 Other tests

*Blood and urine studies*: Complete blood count (CBC), electrolytes, creatinine, blood urea nitrogen (BUN), glucose, and coagulation panel. Erythrocyte sedimentation rate (ESR), while not specific, is elevated in more than 90% of cases. Proteinuria and microscopic hematuria are present in approximately 50% of cases.

*Chest X-ray*: This has a limited value, although it may demonstrate signs of congestive heart failure. Multiple embolic pyogenic abscesses may be visualized.

*Electrocardiography*: This may help detect the 10% of patients who develop a conduction delay during IE by documenting an increased P-R interval. Nonspecific changes are common. A first-degree atrioventricular (AV) block and new interventricular conduction delays may signal septal involvement in aortic valve disease; both are poor prognostic signs.

*Coronary angiography*: This is recommended pre-surgery according to the ESC Guidelines on the Management of Valvular Heart Disease in men over 40 years, in post-menopausal women, and in patients with at least one cardiovascular risk factor or a history of coronary artery disease. Exceptions arise when there are large aortic vegetations that may be dislodged during catheterization, or when emergency surgery is necessary. In these situations, high-resolution CT may be used to rule out significant coronary artery disease.

## 3. Treatment

The major goals of therapy for IE are to eradicate the infectious agent from the thrombus and to address the complications of valvular infection. The latter includes both the intracardiac and extracardiac consequences of IE. Some of the effects of IE require surgical intervention.

### 3.1 Medical treatment

Successful treatment of IE relies on microbe eradication by antimicrobial drugs. Surgery contributes by removing infected material and draining abscesses. Host defenses are of little help. This explains why bactericidal regimens are more effective than bacteriostatic therapy, both in animal experiments and in humans.

Aminoglycosides synergize with cell wall inhibitors (i.e. b-lactams and glycopeptides) for bactericidal activity and are useful for shortening the duration of therapy (e.g. oral streptococci) and eradicate problematic organisms (e.g. *Enterococcus spp.*).

One major hindrance to drug-induced killing is bacterial antibiotic tolerance. Tolerant microbes are not resistant, i.e. they are still susceptible to growth inhibition by the drug, but escape drug-induced killing and may resume growth after treatment discontinuation.

Slow-growing and dormant microbes display phenotypic tolerance towards most antimicrobials (except rifampin to some extent). They are present in vegetations and biofilms, e.g. in PVE, and justify the need for prolonged therapy (6 weeks) to sterilize infected heart valves fully.

Some bacteria carry mutations rendering them tolerant during both active growth and stationary (dormant) phases. Bactericidal drug combinations are preferred to monotherapy against tolerant organisms.

Drug treatment for PVE should last longer (at least 6 weeks) than that for native-valve endocarditis (NVE) (2–6 weeks), but is otherwise similar, except for staphylococcal PVE, for which the regimen should include rifampin whenever the strain is susceptible.

In NVE needing a valve to be replaced by a prosthesis during antibiotic therapy, the postoperative antibiotic regimen should be that recommended for NVE, not for PVE. In both NVE and PVE, the duration of treatment is based on the first day of effective antibiotic therapy, not on the day of surgery.
After surgery, a new full course of treatment should start only if valve cultures are positive, and the choice of antibiotic should be based on the susceptibility of the latest recovered bacterial isolate (Habib et al, 2009).

### 3.1.1 Empirical therapy

IE treatment should be promptly started. The initial choice of empirical treatment depends on several considerations:

- whether the patient has received prior antibiotic therapy or not
- whether the infection affects a native valve or a prosthesis and, if so, when surgery occurred (early vs. late PVE)
- knowledge of local epidemiology, especially for antibiotic resistance and specific genuine culture-negative pathogens.

NVE and late PVE regimens should cover staphylococci, streptococci, HACEK species, and *Bartonella spp.* Early PVE regimens should cover methicillin-resistant staphylococci and, ideally, non-HACEK Gram-negative pathogens (Habib et al, 2009).

| Antibiotic | Dosage and route | Duration (weeks) | Level of evidence | Comments |
|---|---|---|---|---|
| **Native valves** | | | | |
| Ampicillin-sulbactam,<br>or Amoxicillin-clavulanate,<br>with<br>Gentamicin | 12 g/day i.v. in 4 doses<br><br>12 g/day i.v. in 4 doses<br><br><br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses | 4-6<br><br>4-6<br><br><br>4-6 | II C<br><br>II C | Patients with BCNIE should be treated in consultation with an infectious disease specialist. |
| Vancomycin<br>with<br>Gentamicin<br>with<br>Ciprofloxacin | 30 mg/kg/day i.v. in 2 doses<br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses<br>1000 mg/day orally in 2 doses or 800 mg/day i.v. in 2 doses | 4-6<br><br>4-6<br><br>4-6 | II C | For patients unable to tolerate β-lactams<br>Ciprofloxacin is not uniformly active on *Bartonella spp.* Adding doxycycline is an option if *Bartonella spp.* is likely. |
| **Prosthetic valves (early, < 12 months post-surgery)** | | | | |
| Vancomycin<br>with<br>Gentamicin<br>with<br>Rifampin | 30 mg/kg/day i.v. in 2 doses<br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses<br>1200 mg/day orally in 2 doses | 6<br><br>2 | II C | If no clinical response, surgery and maybe extending the antibiotic spectrum to Gram-negative pathogens must be considered. |
| **Prosthetic valves (late, ≥ 12 months post-surgery)** | | | | |
| Same as for native valves | | | | |

Table 2. Proposed antibiotic regimens for initial empirical treatment of IE (before or without pathogen identification) (Adapted from Habib et al, 2009)

### 3.1.2 Penicillin-susceptible oral streptococci and group D streptococci

The cure rate is expected to be > 95%. In uncomplicated cases, short-term (2-week) therapy can be administered by combining penicillin or ceftriaxone with gentamicin or netilmicin. Ceftriaxone alone or combined with gentamicin or netilmicin given once a day is particularly convenient for outpatient therapy. Patients allergic to b-lactams should receive vancomycin. Teicoplanin has been proposed as an alternative and requires loading doses (6 mg/kg/12 h for 3 days) followed by 6–10 mg/kg/day. Loading is critical because the drug is highly bound to serum proteins and penetrates slowly into vegetations.

### 3.1.3 Penicillin-resistant oral streptococci and group D streptococci

Such resistant streptococci are increasing. Antibiotic therapy for penicillin-resistant and penicillin-susceptible oral streptococci is qualitatively similar. However, in penicillin-resistant cases, aminoglycoside treatment may be prolonged to 3–4 weeks, and short-term therapy regimens are not recommended. Little experience exists with highly resistant isolates (MIC > 4 mg/L)—vancomycin might be preferred in such circumstances.

### 3.1.4 *Streptococcus pneumoniae*, b-hemolytic streptococci (groups A, B, C, and G)

IE due to *S. pneumoniae* has become rare since the introduction of antibiotics. It is associated with meningitis in up to 30% of cases, which requires special consideration in penicillin-resistant cases. Treatment is similar to that of oral streptococci, except for the use of short-term (2-week) therapy, which has not been formally investigated. In cases with meningitis, penicillin must be avoided because it poorly penetrates the cerebrospinal fluid, and should be replaced with ceftriaxone or cefotaxime alone or cefotaxime combined with vancomycin.

IE due to group A, B, C, or G streptococci—including the *S. milleri* group (*S. constellatus, S. anginosus,* and *S. intermedius*)—is relatively rare. Group A streptococci are uniformly susceptible to b-lactams, whereas other serogroups may display resistance. IE due to group B streptococci was once associated with the peripartum period, but now occurs in adults, especially the elderly. Group B, C, and G streptococci and *S. milleri* produce abscesses and thus may require adjunctive surgery. The mortality of group B PVE is very high, and cardiac surgery is recommended. Antibiotic treatment is similar to that of oral streptococci, except that short-term therapy is not recommended.

### 3.1.5 Nutritionally variant streptococci

Nutritionally variant streptococci produce IE with a protracted course, which is associated with higher rates of complications and treatment failure (up to 40%), possibly due to delayed diagnosis and treatment. Antibiotic recommendations include penicillin, ceftriaxone, or vancomycin for 6 weeks, combined with an aminoglycoside for at least the first 2 weeks.

### 3.1.6 *S. aureus* and coagulase-negative staphylococci

*S. aureus* is usually responsible for acute and destructive IE, whereas CNS produce more protracted valve infections (except *S. lugdunensis* and some cases of *S. capitis*). *S. aureus* PVE carries a very high risk of mortality (> 45%) and often requires early valve replacement. Other differences in comparison with NVE include the overall duration of therapy, prolonged additional use of aminoglycosides, and the addition of rifampin. Although the level of evidence is poor, adding rifampin in the treatment of staphylococcal PVE is

standard practice, although treatment may be associated with microbial resistance, hepatotoxicity, and drug interactions.

| Antibiotic | Dosage and route | Duration (weeks) | Level of evidence |
|---|---|---|---|
| **Native valves** | | | |
| **Methicillin-susceptible staphylococci** | | | |
| Flucloxacillin<br>or<br>Oxacillin<br>with<br>Gentamicin | 12 g/day i.v. in 4-6 doses<br><br><br><br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses<br>Pediatric doses:<br>Oxacillin or flucloxacillin 200 mg/kg/day i.v. in 4-6 equally divided doses.<br>Gentamicin 3 mg/kg/day i.v. or. i.m. in 3 equally divided doses. | 4– 6<br><br><br><br>3– 5 days | I B |
| **Penicillin–allergic patients or methicillin–resistant staphylococci** | | | |
| Vancomycin<br>with<br>Gentamicin | 30 mg/kg/day i.v. in 2 doses<br><br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses<br>Pediatric doses:<br>Vancomycin 40 mg/kg/day i.v. in 2-3 equally divided doses. | 4– 6<br><br>3– 5 days | I B |
| **Prosthetic valves** | | | |
| **Methicillin–susceptible staphylococci:** | | | |
| Flucloxacillin,<br>or<br>Oxacillin<br>with<br>Rifampin<br>and<br>Gentamicin | 12 g/day i.v. in 4-6 doses<br><br><br><br>1200 mg/day i.v. orally in 2 doses<br><br>3 mg/kg/day i.v. in 2 or 3 doses<br>Pediatric doses:<br>Oxacillin and flucloxacillin as above.<br>Rifampin 20 mg/kg/day i.v. or orally in 3 equally divided doses. | ≥ 6<br><br><br><br>≥ 6<br><br>2 | I B |
| **Penicillin–allergic patients and methicillin-resistant staphylococci:** | | | |
| Vancomycin<br>with<br>Rifampin<br>and<br>Gentamicin | 30 mg/kg/day i.v. in 2 doses<br><br>1200 mg/day i.v. or orally in 2 doses<br><br>3 mg/kg/day i.v. or i.m. in 2 or 3 doses<br>Pediatric doses: As above. | ≥ 6<br><br>≥ 6<br><br>2 | I B |

Table 3. Antibiotic treatment of IE due to *Staphylococcus spp.* (Habib et al, 2009)

### 3.1.7 Methicillin-resistant and vancomycin-resistant staphylococci

MRSA produce low-affinity plasma-binding protein (PBP) 2A, which confers cross-resistance to most b-lactams. They are usually resistant to multiple antibiotics, leaving only vancomycin to treat severe infections. However, vancomycin-intermediate *S. aureus* (VISA) (MIC 4–16 mg/L) and hetero-VISA (MIC ≤ 2 mg/L, but with subpopulations growing at higher concentrations) have emerged worldwide, and are associated with IE treatment failures (Howden et al, 2006). Moreover, some highly vancomycin-resistant *S. aureus* have been isolated from infected patients in recent years, requiring new approaches to treatment. New lipopeptide daptomycin (6 mg/kg/day i.v.) was recently approved for *S. aureus* bacteremia and right-sided IE (Fowler et al, 2006). Observational studies suggest that daptomycin might also be considered in left-sided IE and may overcome methicillin and vancomycin resistance (Levine & Lamp, 2007). Importantly, daptomycin needs to be administered in appropriate doses to avoid further resistance. Other choices include newer b-lactams with relatively good PBP2A affinity, quinupristin-dalfopristin with or without b-lactams, b-lactams plus oxazolidinones, and b-lactams plus vancomycin. Such cases warrant collaborative management with an infectious diseases specialist.

### 3.1.8 *Enterococcus spp.*

Enterococcal IE is primarily caused by *E. faecalis* (90% of cases) and, more rarely, by *E. faecium* or other species. They pose two major problems. First, enterococci are highly tolerant to antibiotic-induced killing, and eradication requires prolonged administration (up to 6 weeks) of synergistic bactericidal combinations of cell-wall inhibitors with aminoglycosides. Secondly, they may be resistant to multiple drugs, including aminoglycosides, b-lactams (via PBP5 modification and sometimes b-lactamases), and vancomycin. Fully penicillin-susceptible strains (penicillin MIC ≤ 8 mg/L) are treated with penicillin or ampicillin (or amoxicillin) combined with gentamicin. Ampicillin (or amoxicillin) might be preferred since MICs are 2–4 times lower. Prolonged courses of gentamicin require regular monitoring of serum drug levels and renal and vestibular function. One study reported success with short-course administration of aminoglycosides (2–3 weeks) in 74 (81%) of 91 episodes of enterococcal IE (Olaison & Schadewitz, 2002). This option might be considered in cases where prolonged treatment is limited by toxicity.

High-level gentamicin resistance is frequent in both *E. faecalis* and *E. faecium*. An aminoglycoside MIC > 500 mg/L is associated with the loss of bactericidal synergism with cell-wall inhibitors, and aminoglycosides should not be used in such conditions. Streptomycin may remain active in such cases and is a useful alternative. An additional recently described (Gavalda et al, 2007) option against gentamicin-resistant *E. faecalis* is the combination of ampicillin and ceftriaxone, which synergize by inhibiting complementary PBPs. Otherwise, more prolonged courses of b-lactams or vancomycin should be considered. B-Lactam and vancomycin resistance are observed primarily in *E. faecium*. Since dual resistance is rare, b-lactam might be used against vancomycin-resistant strains, and vice versa. Varying results have been reported with quinupristin–dalfopristin, linezolid, daptomycin, and tigecycline. Again, these situations require the expertise of an infectious diseases specialist.

### 3.1.9 Gram-negative bacteria

**HACEK-related species**: HACEK Gram-negative bacilli are fastidious organisms needing specialized investigations. Because they grow slowly, standard MIC tests may be difficult to

| Pathogens | Proposed therapy | Treatment outcome |
|---|---|---|
| *Brucella spp.* | Doxycycline (200 mg/24 h) plus cotrimoxazole (960 mg/12 h) plus rifampin (300-600 mg/24 h) for ≥ 3 months orally (Adding streptomycin (15 mg/kg/24 h in two doses) for the first few weeks is optional) | Treatment success defined as an antibody titer < 1:60 |
| *Coxiella burnetii* **(agent of Q fever)** | Doxycycline (200 mg/24 h) plus hydroxychloroquine (200-600 mg/24 h) orally or Doxycycline (200 mg/24 h) plus quinolone (ofloxacin, 400 mg/24 h) orally (>18 months treatment) Doxycycline plus hydroxychloroquine (with monitoring of serum hydroxychloroquine levels) is superior to doxycycline alone and to doxycycline + fluoroquinolone | Treatment success defined as anti-phase I IgG titer < 1:200, and IgM titers < 1:50 |
| *Bartonella spp.* | Ceftriaxone (2 g/24 h) or ampicillin (or amoxicillin) (12 g/24 h) i.v. or Doxycycline (200 mg/24 h) orally for 6 weeks plus Gentamicin (3 mg/24 h) or netilmicin i.v. (for 3 weeks) | Treatment success expected in ≥ 90% |
| *Legionella spp.* | Erythromycin (3g/24h) i.v. for 2 weeks, then orally for 4 weeks plus Rifampin (300-1200 mg/24h) or Ciprofloxacin (1.5 g/24 h) orally for 6 weeks | Optimal treatment unknown. Because of high susceptibility, quinolones should probably be included. |
| *Mycoplasma spp.* | Newer fluoroquinolones (> 6 months treatment) Newer fluoroquinolones are more potent than ciprofloxacin against intracellular pathogens such as *Mycoplasma spp.*, *Legionella spp.*, and *Chlamydia spp.* | Optimal treatment unknown. |
| *Tropheryma whipplei* **(agent of Whipple's disease** | Cotrimoxazole Penicillin (1.2 MU/24 h) and streptomycin (1 g/24 h) i.v. for 2 weeks, then Cotrimoxazole orally for 1 year or Doxycycline (200 mg/24 h) plus *H*ydroxychloroquine (200-600 mg/24 h) orally for ≥ 18 months | Long-term treatment, optimal duration unknown. |

Table 4. Antibiotic treatment of BCNIE. (Adapted from Brouqui & Raoult, 2001)

interpret. Some HACEK group bacilli produce b-lactamases, and ampicillin is therefore no longer the first-line option. Conversely, they are susceptible to ceftriaxone, other third-generation cephalosporins, and quinolones—the standard treatment is ceftriaxone 2 g/day for 4 weeks. If they do not produce b-lactamase, intravenous ampicillin (12 g/day i.v. in four or six doses) plus gentamicin (3 mg/kg/day in two or three doses) for 4 weeks is an option. Ciprofloxacin (2 x 400 mg/day i.v. or 1000 mg/day orally) is a less well-validated option (Das et al, 1997).
**Non-HACEK species**: Recommended treatment is early surgery plus long-term (≥ 6 weeks) therapy with bactericidal combinations of b-lactams and aminoglycosides, sometimes with additional quinolones or cotrimoxazole. *In vitro* bactericidal tests and monitoring serum antibiotic concentrations may be helpful. Because of their rarity and severity, these conditions should be managed with the input of an infectious diseases specialist (Habib et al, 2009).

#### 3.1.10 Blood culture-negative IE
Due to the lack of large series, the optimal duration of the treatment of IE due to these pathogens is unknown. The presented durations are based on selected case reports.
Treating Whipple IE remains highly empirical. Successes have been reported with long-term (> 1 year) cotrimoxazole therapy. γ-Interferon is protective in intracellular infections and has been proposed as adjuvant therapy in Whipple's disease.

#### 3.1.11 Fungi
Fungi are most frequently observed in PVE and in IE affecting IVDAs and immunocompromised patients. *Candida* and *Aspergillus spp.* predominate, the latter resulting in BCNIE. Mortality is very high (> 50%), and treatment necessitates dual antifungal administration and valve replacement. Most cases are treated with various forms of amphotericin B with or without azoles, although recent case reports describe successful therapy with the new echinocandin caspofungin (Garzoni et al, 2007; Lye et al, 2005). Suppressive treatment with oral azoles is often maintained long term and sometimes for life.

### 3.2 Surgical treatment
Surgery has an established role in the management of IE across a wide range of patients, a role that appears poised to increase as the complexity of patients with this difficult condition rises and the benefits of earlier surgery emerge.
Contemporary data in Europe indicate that surgical treatment is used in approximately half of patients with IE because of severe complications. Reasons to consider early surgery in the active phase, i.e. while the patient is still receiving antibiotic treatment, are to avoid progressive heart failure (HF) and irreversible structural damage caused by severe infection and to prevent systemic embolisms. On the other hand, surgical therapy during the active phase of the disease is associated with significant risk.
Surgery performed very early may improve survival in patients with the most severely complicated IE. However, a greater risk of relapses and postoperative valvular dysfunctions should be expected with very early surgery (Thuny et al, 2009).

#### 3.2.1 Indications for surgery in IE
- **Congestive HF**: Congestive HF caused by severe aortic regurgitation or, more rarely, by valve obstruction caused by vegetations, severe acute aortic regurgitation with

echocardiographic signs of elevated left ventricular end-diastolic pressure or significant pulmonary hypertension, congestive HF as a result of prosthetic dehiscence or obstruction;
- **Periannular extension**: Most patients with abscess formation or fistulous tract formation;
- **Systemic embolism**: Recurrent emboli despite appropriate antibiotic therapy, large vegetations (> 10 mm) after 1 or more clinical or silent embolic events after the initiation of antibiotic therapy, large vegetations and other predictors of a complicated course, very large vegetations (> 15 mm) without embolic complications, especially if valve-sparing surgery is likely (remains controversial);
- **Cerebrovascular complications**: Silent neurological complication or transient ischemic attack and other surgical indications, ischemic stroke and other surgical indications, provided that cerebral hemorrhage has been excluded and neurological complications are not severe (e.g. coma);
- **Persistent sepsis:** Fever or positive blood cultures persisting for > 5 to 7 days despite an appropriate antibiotic regimen, assuming that vegetations or other lesions requiring surgery persist and that extracardiac sources of sepsis have been excluded;
- **Relapsing IE:** Especially when caused by organisms other than sensitive streptococci or in patients with prosthetic valves;
- **Difficult organisms:** *S. aureus* IE involving a prosthetic valve and most cases involving a left-sided native valve, IE caused by other aggressive organisms (*Brucella*, *Staphylococcus lugdunensis*), IE caused by multiresistant organisms (e.g. methicillin-resistant *S. aureus* or vancomycin-resistant enterococci) and rare infections caused by Gram-negative bacteria, *Pseudomonas aeruginosa* IE, fungal IE, Q fever IE, and other relative indications for intervention;
- **PVE**: Virtually all cases of early PVE, virtually all cases of PVE caused by *S. aureus*, late PVE with HF caused by prosthetic dehiscence or obstruction (Prendergast & Tornos, 2010).

The three main indications for early surgery in IE are: HF, uncontrolled infection, and prevention of embolic events.

### 3.2.2 Timing of surgery

- **Emergency surgery (within 24 hours):** NVE or PVE and severe congestive HF or cardiogenic shock caused by: acute valvular regurgitation, severe prosthetic dysfunction (dehiscence or obstruction), fistula into a cardiac chamber or the pericardial space
- **Urgent surgery (within days):** NVE with persistent congestive HF, signs of poor hemodynamic tolerance, or abscess; PVE with persistent congestive heart failure, signs of poor hemodynamic tolerance, or abscess; PVE caused by staphylococci or Gram-negative organisms, large vegetation (> 10 mm) with an embolic event, large vegetation (> 10 mm) with other predictors of a complicated course, very large vegetation (> 15 mm), especially if conservative surgery is available, large abscess or periannular involvement with uncontrolled infection;
- **Early elective surgery (during the in-hospital stay):** Severe aortic regurgitation with congestive HF and good response to medical therapy, PVE with valvular dehiscence or congestive heart failure and good response to medical therapy, presence of abscess or periannular extension, persistent infection when extracardiac focus has been excluded, fungal or other infections resistant to medical cure (Prendergast & Tornos, 2010).

### 3.2.3 Surgical approach and techniques

The two primary objectives of surgery are the total removal of infected tissue and the reconstruction of cardiac morphology, including repair or replacement of the affected valve.
The mode of surgery (replacement versus repair) or type of prosthesis used (mechanical versus biological) has no influence on operative mortality, although repair techniques, when applicable, offer long-term advantages, including a reduced risk of late complications (notably, recurrent IE) and obviate the need for lifelong anticoagulation medication. Homografts offer a reduced risk of recurrent infection in aortic IE, although their use remains controversial owing to a higher risk of late complications. Cardiac transplantation may be considered in extreme cases with recurrent PVE (Pavie, 2006).
Where infection is confined to the valve cusps or leaflets, any method of repairing or replacing the valve may be used. However, valve repair is favored whenever possible. Perforations in a single valve cusp or leaflet may be repaired with an autologous glutaraldehyde-treated or bovine pericardial patch.
In complex cases with locally uncontrolled infection, total excision of infected and devitalized tissue should be followed by valve replacement and repair of associated defects to secure valve fixation. Mechanical and biological prostheses have similar operative mortality (Edwards et al, 1998). The use of foreign material should be kept to a minimum. Small abscesses can be closed directly. Radical resection of the abscess is essential. The general consensus is that an aortic valve homograft is the ideal conduit for an aortic root abscess, but that it is not a substitute for radical extirpation of the abscess and all inflamed tissue (David et al, 2007).
In aortic IE, replacing the aortic valve with a mechanical or biological prosthesis is the technique of choice. Using cryopreserved or sterilized homografts has been suggested to reduce the risk of persistent or recurrent infection (Lopes et al, 2007). However, mechanical prostheses and xenografts compare favorably, and with improved durability. Homografts or stentless xenografts may be preferred in PVE or in cases where there is extensive aortic root destruction with aorto-ventricular discontinuity (Sabik et al, 2002). A tailored tubular Dacron graft to concomitantly reconstruct the left ventricular outflow tract and replace the aortic root is a useful and safe operative technique for patients with destroyed aorto-ventricular junction.
A monoblock aorto-mitral homograft has been suggested as a surgical option for extensive bivalvular IE (Obadia et al, 2006).

### 3.2.4 Operative mortality and morbidity

Perioperative mortality and morbidity vary according to the type of infective agent, the extent of destruction of cardiac structures, the degree of left ventricular dysfunction, and the patient's hemodynamic condition at the time of surgery. Currently, operative mortality in IE lies between 5% and 15%.
The outcomes of PVE are worse than those of NVE. The main reason the operative mortality for PVE is higher than that for NVE is the complexity of the operation and the fact that it is often associated with a paravalvular abscess (David et al, 2006).
When surgery must be done within the first week of antimicrobial therapy, a recent study showed that in-hospital mortality is 15%, with risks of recurrence and non-infective postoperative valvular dysfunction of 12% and 7%, respectively (Thuny et al, 2008).
In less complex cases, where disease is limited to the valve structures alone allowing complete excision of the infected tissue, mortality should be similar to routine valve surgery.

The cause of death is often multifactorial, but the main reasons are multiorgan failure, HF, intractable sepsis, coagulopathy, and stroke.

#### 3.2.5 Postoperative complications

Immediate postoperative complications are relatively common. Among the most frequent are severe coagulopathy requiring treatment with clotting factors, re-exploration of the chest for bleeding or tamponade, acute renal failure requiring hemodialysis, stroke, low cardiac output syndrome, pneumonia, and atrioventricular block following radical resection of an aortic root abscess with a need for pacemaker implantation. A preoperative ECG demonstrating left bundle branch block predicts the need for a postoperative permanent pacemaker.

### 3.3 Prophylaxis for IE

The European Society of Cardiology Guideline proposes limiting antibiotic prophylaxis to patients with the highest risk of IE undergoing the highest risk dental procedures. Patients with the highest risk of IE are patients with a prosthetic valve or a prosthetic material used for cardiac valve repair, patients with previous IE, patients with congenital heart disease, in particular those with complex cyanotic heart disease and those who have postoperative palliative shunts, conduits, or other prostheses. Procedures at risk involve the manipulation of the gingival or periapical region of teeth or perforation of the oral mucosa, including scaling and root canal procedures. Good oral hygiene and regular dental review are very important for reducing the risk of IE. Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of healthcare-associated IE (Habib et al, 2009).

The American Heart Association Guideline includes cardiac transplant recipients who develop cardiac valvulopathy on the list of patients with the highest risk of IE. It also recommends prophylaxis for procedures on respiratory tract or infected skin, skin structures, or musculoskeletal tissue only for patients with underlying cardiac conditions associated with the highest risk of adverse outcome from IE (Wilson et al, 2007).

An antibiotic for prophylaxis should be given in a single dose 30-60 minutes before the procedure. Amoxicillin is the preferred choice for oral therapy because it is well absorbed in the GI tract and provides high and sustained serum concentrations. For individuals who are allergic to penicillin or amoxicillin, the use of cephalexin or another first-generation oral cephalosporin, clindamycin, azithromycin, or clarithromycin is recommended. Because of possible cross-reactions, a cephalosporin should not be given to patients with a history of anaphylaxis, angioedema, or urticaria after treatment with any form of penicillin, including ampicillin or amoxicillin (Habib et al, 2009; Wilson et al, 2007).

## 4. Complications of IE

### 4.1 Heart failure

HF is the most frequent complication of IE and represents the most frequent indication for surgery in IE. HF is observed in 50–60% of cases overall and is more often present when IE affects the aortic (29%) rather than the mitral (20%) valve (Baddour et al, 2005). HF can be caused by severe aortic regurgitation, intracardiac fistulae, or, more rarely, by valve obstruction, when a large vegetation partially obstructs the valve orifice.

Clinical presentation of HF may include severe dyspnea, pulmonary edema, and cardiogenic shock. In addition to clinical findings, TTE is crucially important for the initial evaluation and follow-up. Echocardiography is also of more general value for hemodynamic assessment of valvular dysfunction, measurement of pulmonary artery pressure, and assessment and monitoring of left ventricular systolic function and left and right heart filling pressures. Brain natriuretic peptide (NT-proBNP) is potentially useful for diagnosing and monitoring HF in IE.

HF may progress from mild to severe during treatment, and two-thirds of these cases occur during the active phase of the disease. Moderate-to-severe HF is the most important predictor of in-hospital and 6-month mortality (Baddour et al, 2005).

### 4.2 Uncontrolled infection

Uncontrolled infection is the second most frequent cause for surgery and encompasses persisting infection (> 7–10 days), infection due to resistant organisms, and locally uncontrolled infection.

Uncontrolled infection is most frequently related to perivalvular extension (the most frequent cause, associated with a poor prognosis and a high likelihood of the need for surgery) or difficult-to-treat organisms, such as fungi, multiresistant organisms, e.g. MRSA or vancomycin-resistant enterococci, and also in the rare infections caused by Gram-negative bacteria.

Signs of locally uncontrolled infection include increasing vegetation size, abscess formation, false aneurysms, or the creation of fistulae. Persistent fever is also usually present.

Unless severe comorbidity exists, the presence of locally uncontrolled infection indicates early surgery in patients with NVE (Habib et al, 2009).

### 4.3 Systemic embolism

Embolic events are a frequent and life-threatening complication of IE related to the migration of cardiac vegetations. It has been reported to occur in 13% to 49% of cases. The brain and spleen are the most frequent sites of embolisms in aortic IE.

Embolisms after adequate antimicrobial treatment are frequent, and most embolisms occur within the first two weeks of therapy. Embolisms before antimicrobial therapy are a risk factor for embolisms after antimicrobial therapy has begun. Controlling infection is important for preventing embolisms. The benefits of surgery to prevent embolisms are greatest during the first week of antibiotic therapy, when embolic risk peaks.

Several factors are associated with increased risk of embolisms: the size and mobility of vegetations, the location of the vegetation, an increase or decrease in the size of the vegetation under antibiotic therapy, particular microorganisms (staphylococci, *Streptococcus bovis*, *Candida spp.*), previous embolisms, multivalvular IE, and biological markers.

The risk of embolization seems to increase with increasing vegetation size, and this is particularly significant in staphylococcal endocarditis (Vilacosta et al, 2002).

### 4.4 Neurological complications

Neurologic events develop in 20–40% of all patients with IE.

Neurologic complications of IE most commonly occur as a result of embolization from endocardial vegetation, with the resultant occlusion of cerebral arteries. An ischemic or hemorrhagic stroke or a transient ischemic attack (TIA) can then develop. The dissemination of infected embolic material into cerebral or meningeal vessels may also lead to meningitis

or brain abscesses. More nonspecific neurologic manifestations associated with IE include headache, seizures, and toxic encephalopathy. Cerebral hemorrhage is the most dramatic, though fortunately rare, neurologic complication of IE. It can be caused by a rupture of a mycotic aneurysm even months to years after the IE has been cured.
Neurologic manifestations of IE occur mainly before antimicrobial treatment has begun, thus reinforcing the belief that rapidly diagnosing and initiating antimicrobial therapy may still be the most effective means of preventing neurologic complications (Heiro et al, 2000).
After a first neurological event, most patients still have an indication for surgery that is generally not contraindicated.

### 4.5 Infectious aneurysms

Infectious (mycotic) aneurysms (IAs) result from septic arterial embolisms to the intraluminal space or vasa vasorum, or from the subsequent spread of infection through the intimal vessels. An intracranial location is most frequent, and the reported frequency of 2–4% (Corr et al, 1995) is probably an underestimate since some IAs are clinically silent.
The most important sequelae of these aneurysms is bleeding, which can occur days, weeks, months, or, rarely, years after successful therapy for the underlying IE. Cerebral mycotic aneurysms tend to occur in the more distal portions of the middle cerebral artery near the surface of the brain involving the secondary and tertiary branches. This characteristic pattern helps to separate them clinically from berry aneurysms, which tend to occur near the base of the brain and the circle of Willis.

### 4.6 Acute renal failure

Acute renal failure is a common complication of IE, which occurs in 30% of patients and predicts a poor prognosis. Causes of acute renal failure are often multifactorial and include the following: immune complex and vasculitic glomerulonephritis, renal infarction, hemodynamic impairment in cases with HF or severe sepsis, or, after cardiac surgery, antibiotic toxicity, notably related to aminoglycosides, vancomycin, and even high-dose penicillin, nephrotoxicity of contrast agents used for imaging (Majumdar et al, 2000).
Hemodialysis may be required in some patients, but acute renal failure is often reversible.

### 4.7 Rheumatic complications

Musculoskeletal symptoms (arthralgia, myalgia, back pain) are frequent during IE, and rheumatic complications may be the first manifestations of the disease. Peripheral arthritis occurs in 14% and spondylodiscitis in 3–15% of cases.
Vertebral osteomyelitis is a known but rare complication of IE, occurring most frequently in patients with *S. aureus* infection. Acute septic arthritis involving 2 or more joints should raise a suspicion of IE (Speechly-Dick & Swanton, 1994).

### 4.8 Splenic abscess

Although splenic emboli are common, splenic abscess is rare. Persistent or recurrent fever and bacteremia suggest the diagnosis, and these patients should be evaluated using abdominal CT, MRI, or ultrasound. Treatment consists of appropriate antibiotic regimens. A splenectomy may be considered for splenic rupture or large abscesses that respond poorly to antibiotics alone, and should be done before valvular surgery, unless the latter is urgent. Percutaneous drainage is an alternative for high-risk surgical candidates. (Chou et al, 1992)

### 4.9 Myocarditis, pericarditis

Cardiac failure may also be due to myocarditis, which is frequently associated with abscess formation. Regional myocardial infarction may be caused by coronary embolisms or compression. Ventricular arrhythmias may indicate myocardial involvement and imply a poor prognosis. Myocardial involvement is best assessed using TTE.

Pericarditis may be associated with an abscess, myocarditis, or bacteremia, often as a result of *S. aureus* infection. Purulent pericarditis is rare and may necessitate surgical drainage. Rarely, ruptured pseudoaneurysms or fistulae may communicate with the pericardium, with dramatic and often fatal consequences (Sexton & Spelman, 2002).

## 5. Outcome and long-term prognosis

The prognosis of aortic valve endocarditis depends largely on when the disease is diagnosed, which microorganism is involved, and how promptly it is treated.

Patients with PVE have a more serious prognosis than patients with NVE.

Late complications occurring after the initial infection contribute to the poor prognosis of IE. Following in-hospital treatment, the main complications include a recurrence of infection, HF, a need for valve surgery, and death.

The risk of recurrence among survivors of IE varies between 2.7% and 22.5%. There are two types of recurrence: relapse and reinfection. The term "relapse" refers to a repeat episode of IE caused by the same microorganism as the previous episode. In contrast, "reinfection" is used primarily to describe infection with a different microorganism (Chu et al, 2005). Relapses are most often due to an insufficient duration of the original treatment, a suboptimal choice of initial antibiotics, and a persistent focus of infection (e.g. a periprosthetic abscess).

Progressive HF can occur as a consequence of valve destruction, even when the infection is healed. After the completion of treatment, recommendations for surgery follow conventional guidelines.

Following the in-hospital phase, principal factors that determine long-term mortality are age, comorbidity, and HF, particularly when surgery has not been done, which suggests that long-term mortality is related to the underlying conditions rather than to the IE itself.

A high early surgery rate is related to good long-term results and does not increase in-hospital mortality. Medical treatment, however, also offers favorable long-term results in cases of responsive IE where poor prognostic factors are absent (Bishara et al, 2001).

The IE prognosis is not uniform. Mortality is high during the initial phase, but after one year, the risk of dying is low, although still above that of the general population. Part of the risk is probably the direct consequence of IE, but part is due to the course of the underlying heart disease (Delahaye et al, 1995).

## 6. Conclusions

IE is a changing disease with predisposing risk factors, etiology, manifestations, and therapeutics in continuous evolution.

Although modern antibiotic and surgical treatments have substantially improved outcomes in recent decades, IE remains a life-threatening disease. As mortality during the active phase of the infection has declined, long-term morbidity and mortality caused by late sequelae

such as congestive HF, valve incompetence, and predisposition to recurrent IE are becoming more important. Moreover, the focus has shifted away from infections of native valves to endocarditis of prosthetic valves in the elderly and to endocarditis in users of injected drugs. Effective therapy has become progressively more difficult to achieve because of the proliferation of implanted biomechanical devices and the rise in the number of resistant organisms.

Endocarditis has evolved into several variations, keeping it near the top of the list of diseases that must not be misdiagnosed or overlooked.

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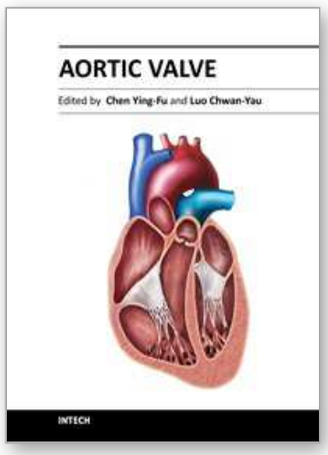
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**Aortic Valve**

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Much has evolved in the field of aortic valve disease because of the increase in knowledge in the last decade, especially in the area of its management. This book "Aortic Valve" is comprised of 18 chapters covering basic science, general consideration of aortic valve disease, infective endocarditis, aortic sclerosis and aortic stenosis, bioprosthetic valve, transcatheter aortic valve implantation and a special section on congenital anomalies of the aortic valve. We hope this book will be particularly useful to cardiologists and cardiovascular surgeons and trainees. We also believe that this book will be a valuable resource for radiologists, pathologists, cardiovascular anesthesiologists, and other healthcare professionals who have a special interest in treating patients with aortic valve disease. We are certain that information in this book will help to provide virtually most new areas of aortic valve disease that will be employed in the current era.

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