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# Aortic Valve Endocarditis

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## 1. Introduction

Infective endocarditis (IE) is an endovascular infection of cardiovascular structures – usually valves – but also large intra-thoracic vessels and intra-cardiac foreign bodies. It is typically caused by bacteria or fungi. In contrast, sterile thrombotic lesions are termed non-bacterial thrombotic endocarditis (NBTE). IE is generally characterised by lesions of vegetations composed of platelets, fibrin, microorganisms, and inflammatory cells, as well as leaflet disruption to a various degree. Endocarditis may also produce a wide variety of systemic signs and symptoms due to sterile and infected emboli, as well as various immunological phenomena. IE is a fatal disease if left untreated (Horstkotte et al., 2004).

Characterising aspects of IE were first described by Jean François Fernel in his book Medicini in 1554. Lazaire Riviere followed suit with gross autopsy findings of the disease in 1723 after which, in 1852, Kirkes described emboli arising from heart valves in cerebral, renal, splenic and other arteries. Although several reports of IE have been published since – some from well-known physicians like Morgagni and Virchow, it was not until 1885 that IE was comprehensively documented when Sir William Osler accumulated various works and presented them to the public in the form of the comprehensive analysis of this disease (Millar & Moore, 2004).

Despite substantial improvements in diagnosis and treatment of native valve IE, disease incidence is on an increase currently averaging 3.3 new cases each year per 100,000 population in the United Kingdom, similar figures in the United States, and 1.4 to 4 new cases over the same population in European countries (Bashore et al., 2006). Native valve IE continues to be associated with high morbidity and mortality rate. Even though IE was previously associated with poor dentition and rheumatic heart disease, many factors have altered its epidemiology but have maintained its incidence: an aging population with degenerative valvular disease, injection drug use, increasing number of valve replacements, and medical interventions i.e. invasive vascular procedures (Wang & Bashore, 2009). Several variants to valve endocarditis have also been recognized: nosocomial IE, intravenous drug abuse IE, and prosthetic valve endocarditis (PVE). Nosocomial infective endocarditis is defined as acute IE, occurring 48 to 72 hours or more post-admission to hospital, or endocarditis directly related to a hospital-based procedure performed during a prior hospital visit within eight weeks of admission (Haddad et al., 2004). Intravenous drug abuse IE most commonly affects tricuspid valve and is associated with no previous structural damage of the valve. PVE accounts for 10-20% of cases. Incidence of PVE is reported to be most often between 0.2 and 0.8% for each year of life with an implanted valve (Dominik &

Zacek, 2010). Two forms of PVE can be distinguished: early PVE that occurs within 60 days of valve implantation, and late PVE occurring 60 days or more after valve implantation. It is more common after aortic than after mitral valve replacement and affects mechanical and bioprosthetic valves equally (Baddour & Wilson, 2005).

IE may give rise to numerous extracardiac, cardiac, and valvular findings, including infected thrombi (vegetations), sequel of local tissue destruction, and systemic manifestations including vasculitis, emboli, and ischemic events (Kwan-Leung & Embli, 2006). The classic clinical presentation of IE may be characterized as acute or subacute-chronic. Acute IE develops abruptly and progresses rapidly irrespective of person's health or debilitation level. A source of infection or portal of entry is often evident. When bacteria are virulent or bacterial exposure is massive, acute IE can affect normal valves. It is usually presented with signs of hemodynamic deterioration due to valve destruction caused by more aggressive forms of pathogens. The course of subacute IE is more subtle yet harder to diagnose, and may extend over many months. Often no source of infection or portal of entry is evident.

Nowadays, echocardiography offers a highly accurate diagnostic mechanism aimed at early detection and recognition of this disease and its complications also in the absence of positive blood cultures. Trans-esophageal echo (TEE) is preferred over trans-thoracic echo (TTE) because of its high sensitivity and greater ability to visualize local spread of infection at an early stage. Valve incompetence with left ventricular decompensation and congestive heart failure is the usual hemodynamic complication. Surgically demanding cases are those that affect periannular tissue and lead to significantly increased mortality and the rate of recurrent infection (Knosalla et al., 2000). Local spread of infection occurs in about 10 to 40% of native valve IE (Kang et al., 2009). Potential complications from a periannular progression of IE include abscess formation, pseudoaneurysm formation of the mitral-aortic interventricular fibrosa and the subsequent development of aorto-cavitary fistula (ACF). It is estimated that 1.5-2.2% of the patients with IE of aortic valve will develop ACF, more frequently those with prosthetic valve IE than those with native valve IE (odds 1.61:1) (Anguera et al., 2005). ACF is the most dangerous complication of periannular tissue involvement with the mortality of up to 40%. Extension of the IE from aortic to the mitral valve is possible and occurs through mitro-aortic fibrous continuity with development of a septic aneurysm in the anterior mitral leaflet with or without perforation.

## 2. Pathogenesis

Several conditions must be met in order to develop IE. According to the injury-thrombus-infection theory, the trigger event is the endocardium damage. Endothelial injury is the most plausible factor leading to platelet deposition. Injury develops as a result of hemodynamic and mechanical stress to the endocardium. The predilection site of IE is rough part of the valves (the coaptation area) due to high impact pressures following the closure of the leaflets. Also, turbulent blood flow produced by congenital or acquired heart diseases traumatizes the endothelium inducing apoptosis of valve cells and leading to tissue remodelling. As a result, platelet and fibrin deposition occurs. The phase in which sterile thrombotic vegetations are present on the leaflets is referred to as NBTE. The Venturi effect also contributes to the development and location of NBTE, i.e. vegetations are attached to the flow side of the valves (ventricular side of semilunar valves, tips of the leaflets, sewing rings of prosthetic valves) (Bashore et al., 2006). The entry of micro-organisms into the

circulatory system leads to bacteremia and ultimately converts NBTE into IE. Naturally this would depend on the bacteria inoculum sufficient to allow invasion of the pre-existing valve thrombus. Clinical manifestation of IE appears to be influenced by several factors both host and pathogen related (susceptibility of the host genetically determined by defence mechanisms and adherence propensity as well as invasiveness of certain pathogens) (Naber et al., 2009).

On gross examination, vegetations are usually grey, pink, or brown and are often friable. They may be single or multiple and may affect more than one valve. Vegetations may be located anywhere on the valve cusp or leaflet or endocardial surface. In fact this is an important distinguishing feature to note, as valve thrombi associated with nonbacterial thrombotic endocarditis (NBTE) and those related to rheumatic fever do not have this variability in location, and are usually along the lines of valve closure (Kwan-Leung & Embli, 2006). Corresponding microscopic finding would depend on the virulence and duration of the induction and is usually characterized with presence of fibrin, neutrophils and clumps of organisms with foci of calcification or organized thrombi to a certain extent.

### 2.1 Microbiology

The common causes of native valve IE include members of the normal bacterial flora of the skin, oropharynx and the gastrointestinal and genitourinary tract (Kwan-Leung & Embli, 2006). The most common microorganisms that cause IE include: *Streptococci, Staphylococcus aureus, Enterococcus* species, HACEK organisms (*Hemophilus parainfluenzae, Hemophilus aphrophilus, Actinobacillus actinomycetemcomitans, Cardiobacterium hominis, Eikenella* species, and *Kingella* species) and fungi (Bayer et al., 1998). *S. aureus* is more often associated with the native valve IE than PVE, whereas coagulase negative *Staphyloococci* are more commonly seen in PVE. Furthermore, *Enterococcus spp*. usually leads to subacute form of IE. Anaerobic bacteria are rarely associated with IE and account 2-16% of all cases (Brook, 2008). *Candida* and *Aspergillus* species cause the majority of fungal IE (Bayer et al., 1998). Intravenous drug abusers, prosthetic-valve recipients, and patients with long-term central venous catheters are at highest risk for fungal IE. Fungal infected thrombi are usually quite large and friable leading to valve orifice obstruction.

| Procedure | Rate | Micro-organisms |
|---|---|---|
| Endoscopy | 0-20% | Coagulase negative Staphylococi, Streptococci, diphteroids |
| Colonoscopy | 0-20% | Escherichila coli, Bacteroides species |
| Barium enema | 0-20% | Enterococci, aerobic and anaerobic gram-negative rods |
| Dental extractions | 30-100% | Streptococcus viridans |
| Transurethral resection of the prostate | 20-45% | Coliforms, Enterococci, Staphylococcus aureus |
| Transesophageal echocardiography | 0-25% | Streptococcus viridans, anaerobic organisms, Streptococci |

Table 1. Rate of subsequent bacteraemia following certain procedures

Microorganisms have surface adhesions that mediate the adherence to vegetation and avidly bind to valvular and peri-annular tissue with irreversible adhesion (Mocchegiani & Nataloni, 2009). They then produce a biofilm that inhibits host's defence mechanisms and to protect themselves against antimicrobial treatment. This makes antibiotic sterilization extremely difficult. Causative microorganisms vary by site of infection, source of bacteremia, and host risk factors as shown in Table 1 (Towns & Reller, 2003).

Blood culture negative endocarditis (BCNE) is by definition IE in which standard culture methods are inadequate to allow detection of the causative agents. The incidence of BCNE have historically ranged from 2.5% to 31% depending on the study population (Kwan-Leung & Embli, 2006). The most common pathogens that cause BCNE are: *Coxiella burnetti*, *Bartonella spp.* and *Trophyrema whipplei.* IE associated with these microorganisms most often occurs in patients with some form of immunodeficiency, valvular disease and a history of contact with domestic animals.

## 3. Clinical presentation and diagnosis

The diagnosis of IE is based upon clinical suspicion derived from signs and symptoms and most importantly the demonstration of associated bacteremia. Clinical presentation of IE may vary significantly with regards to causative pathogen, immunological status of the host, intermittent use of antibiotics, structural heart disease, and presence of foreign objects (heart valves, pacemakers etc.). The diagnosis of IE is straightforward in those patients with classic manifestations: bacteremia or fungemia, evidence of active valvulitis, peripheral emboli, and immunologic vascular phenomena (Bayer et al., 1998). In other patients however the classic peripheral stigmata may be few or absent. All this imposes the necessity for highly sensitive diagnostic algorithm that will be both sensitive for disease detection and specific for its exclusion across all the forms of the disease (Baddour et al., 2005).

Initial signs and symptoms of subacute IE may be vague and ambiguous: low grade fever, fatigability and malaise, night sweats, and weight loss. Clinical manifestation may be prolonged until the development of a heart murmur with or without signs of valvular insufficiency. From this point on, diagnosis can be readily established. However, majority of the patients already have detectable heart murmurs and with a coinciding clinical presentation, IE should be suspected. Peripheral lesions of subacute IE include: petechiae (oral mucosa, conjunctivae, the dorsa of the hands and feet, chest and abdominal wall), subungal haemorrhages (splinter haemorrhages), Osler nods, clubbing fingers, Roth spots (round or oval haemorrhagic retinal lesions), Janeway lesions (irregular erythematous and painless macules on palms and soles). In current times of widespread use of antibiotics, incidence of classic presentation of the peripheral lesions reduced substantially. Some of the peripheral manifestations develop as a result of immunological activities, while others result from embolization. About 35% of patients may develop central nervous system effects such as transient ischemic attacks, stroke, toxic encephalopathy, and brain abscess (Baddour et al., 2005). Renal embolization may lead to hematuria while splenic emboli may cause left upper quadrant pain.

Acute IE is characterized by a more rapid and progressive course of the disease. The invasiveness and aggressiveness of the pathogen causes prompt reaction in the host including hyperpyrexia, profuse sweating, fatigue, and malaise. Signs and symptoms of heart failure develop very often and heart murmur is present in almost every case.

| Definite IE |
|---|
| Pathological criteria |
| Microorganisms demonstrated by culture or histological examination of a vegetation, a vegetation that has embolized, or an intracardiac abscess specimen; or<br>Pathological lesions; vegetation or intracardiac abscess confirmed by histological examination showing active endocarditis |
| Clinical criteria |
| 2 major criteria; or<br>1 major criterion and 3 minor criteria; or<br>5 minor criteria |
| Possible IE |
| 1 major criterion and 1 minor criterion; or 3 minor criteria |
| Rejected |
| Firm alternative diagnosis explaining evidence of IE; or<br>Resolution of IE syndrome with antibiotic therapy for 4 days; or<br>No pathological evidence of IE at surgery or autopsy, after antibiotic therapy for 4 days; or<br>Does not meet criteria for possible IE as above |

Table 2. Definition of IE according to the modified Duke criteria (Li et al., 2000)

| Major blood culture criteria include |
|---|
| Two blood cultures positive for organisms typically found in patients with IE (i.e., *S viridans, Streptococcus bovis,* a HACEK group organism, community-acquired *S aureus,* or *Enterococci* in the absence of a primary focus) |
| Blood cultures persistently positive for one of the above organisms from cultures drawn more than 12 hours apart |
| Three or more separate blood cultures drawn at least 1 hour apart |
| Single positive blood culture for *Coxiella burnetii* or anti–phase 1 IgG antibody titer > 1:800 |
| Major echocardiographic criteria include |
| Echocardiogram positive for IE, documented by an oscillating intracardiac mass on a valve or on supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation |
| Myocardial abscess |
| Development of partial dehiscence of a prosthetic valve |
| New-onset of valvular regurgitation |
| Minor criteria include |
| predisposing heart condition |
| fever |
| temperature > 38$^{o}$ |
| vascular phenomena or immunologic phenomena |
| microbiological evidence that does not meet a major criteria |

Table 3. Definition of terms used in the modified Duke criteria for IE diagnosis (Li et al., 2000)

With regard to recurrence of IE, two types are described: relapse – repeat episodes of IE caused by the same microorganism < 6 months after the initial episode; and reinfection – infection with a different microorganism or repeat episode of IE caused by the same microorganism > 6 months after the initial episode.
IE diagnostic criteria published in the previous studies were refined by Durack and colleagues from Duke University Medical Center in 1994. These criteria, which have come to be known as the Duke criteria, incorporated echocardiographic evidence of endocardial involvement (Table 2, Table 3) (Durack et al., 1994; Li et al., 2000). The criteria had improved test performance characteristics over the prior set and have been validated subsequently by many other studies (Wang & Bashore, 2009).
European society of cardiology published diagnostic criteria that should raise suspicion of IE (Table 4) (Horstkotte et al., 2004). These overlap the Duke criteria to an extent, but are also notably different.

| |
|---|
| High clinical suspicion (urgent indication for echocardiographic screening and possibly hospital admission) |
| new valve lesion/(regurgitant) murmur |
| embolic event(s) of unknown origin (esp. cerebral and renal infarction) |
| sepsis of unknown origin |
| haematuria, glomerulonephritis, and suspected renal infarction |
| fever plus one or more of these: |
| prosthetic material inside the heart; other high predispositions for IE; newly developed ventricular arrhythmias or conduction disturbances; first manifestation of CHF; positive BCs (if the organism identified is typical for NVE/PVE); cutaneous (Osler, Janeway) or ophthalmic (Roth) manifestations; multifocal/rapid changing pulmonic infiltrations (right heart IE); peripheral abscesses (renal, splenic, spine) of unknown origin; predisposition and recent diagnostic/therapeutic interventions known to result in significant |
| Low clinical suspicion |
| fever plus none of the above |
| *IE – Infective endocarditis; CHF – Congestive heart failure; BC – Blood cultures; NVE – Native valve endocarditis; PVE – Prosthetic valve endocarditis* |

Table 4. Criteria that should raise suspicion of IE (Horstkotte et al., 2004)

Although differential diagnosis may seem abundant, after careful clinical management it can be reduced to: non-infectious endocarditis (marantic endocarditis – paraneoplastic syndrome associated with some malignancies and Libman-Sacks endocarditis – associated with systemic lupus erythematosis), and cardiac tumors (atrial myxoma and valve fibroelastoma) (Velicki et al., 2010).

### 3.1 Echocardiography

Echocardiography plays a crucial role in the diagnosis and management of IE. Diagnosis should be based on the isolation of the microorganism through the blood cultures. In certain cases blood cultures would yield inadequate (non-diagnostic) results due to changing nature of valvular infection necessitating reliance on echocardiography as an indirect diagnostic method. Echocardiography is useful not only for assessing the structural and functional

valvular status, but also for the local spread of infection (annular abscess or ACF), as well as predicting the potential for embolization. Echocardiography should be performed in all cases of suspected IE (Baddour et al., 2005).
In most cases TTE would be sufficient in evaluation of aortic valve endocarditis. TEE may be indicated in case of PVE suspicion, evaluation of local spread of infection (better visualization of abscess cavities and ACF), as well as predicting embolization potential based on the vegetation size, consistency, location, number and mobility. Both TTE and TEE can produce false-negative and false-positive results on rare occasions (too small vegetations or already dislodged vegetations, valvular abnormalities not related to a current infection, respectively). Echocardiography should therefore be only one step in a diagnostic chain. More recent studies have shown that in majority of clinical situations of suspected IE, an initial strategy of TEE is more cost-effective than a staged procedure with TTE and is therefore an optimal strategy over empiric antibiotic therapy alone (Habib et al., 2009). At the same time it is important to outline specific definitions of the echocardiographic findings to adequately evaluate local endocarditis presentation (Table 5) (Sachdev et al., 2003).

| Finding | Description |
|---|---|
| Vegetation | Irregularly shaped, discrete echogenic mass, adherent to but distinct from endocardial surface or intra-cardiac device<br>Oscillation of mass (supportive, not mandatory) |
| Abscess | Thickened area or mass within the myocardium or valve annulus, or evidence of flow into region (supportive, not mandatory) |
| Aneurysm | Echolucent space with thin surrounding tissue |
| Fistula | Blood flow between two distinct cardiac blood spaces or chambers through abnormal path/channel |
| Leaflet perforation | Defect in body of valve leaflet with flow through defect |
| Valve dehiscence | Prosthetic valve with abnormal rocking motion/excursion in at least one direction |

Table 5. Echocardiographic findings in IE and corresponding definitions (Sachdev et al., 2003)

### 3.2 Periannular extension

Periannular extension of infection is one of the most fearful complications in patients with IE. Perivalvular extension in the setting of native valve IE develops from bacterial necrosis of local tissue and results in high rates of heart failure and death despite surgical therapy (Anguera et al., 2006). Local spread of infection occurs in about 10 to 40% of native aortic valve endocarditis (Kang et al., 2009).
Periannular abscess formation and aortocavitary fistulous tract formation in IE represent a further step in aortic annular erosion and the extension of infection beyond the leaflets and the aortic ring. In the early stage, perivalvular abscess is largely composed of inflammatory infiltrate, but at later stages necrosis and cavitation usually develop leading to destruction of perivalvular tissue. Perivalvular abscess is not a static complication but is progressive and can evolve into serious perivalvular complications including perivalvular leak, fistula and pseudoaneurysm (Kwan-Leung & Embli, 2006). It is estimated that 1.5-2.2% of patients with IE of aortic valve will develop ACF, and even more frequently those with PVE as opposed to those with native valve endocarditis (odds 1.61:1) (Anguera et al., 2005). Due to the central

position of the aortic valve, infection of the valve may form fistulas with practically any surrounding chamber (Susak et al., 2009). Because PVE usually begins as periannulitis, it is not surprising that infected prosthetic valves have these complications with a higher frequency than native valves. ACF is the most dangerous complication of periannular tissue involvement with the mortality of up to 40% (Kang et al., 2009). It is estimated that around 60% of patients with ACF develop heart failure before surgery and the extent of the heart failure is more severe than in patients with nonruputred abscesses (Anguera et al., 2006). Extension of the IE from aortic to the mitral valve occurs through mitro-aortic fibrous continuity with development of a septic aneurysm in the anterior mitral leaflet with or without perforation. Myocardial ischemic sequelae may develop as a result of debris embolization from aortic root abscess, or due to extraluminal compression from an enlarged aortic root abscess. Coronary arteries can become directly affected by local extension through the coronary ostia or by creation of mycotic aneurysms.

In the published data, one of the most convincing and consistently reliable variables predictive of periannular complications has been the appearance of an AV block and signs of pericarditis or pericardial effusion (Graupner et al., 2002). Most of these patients will undergo surgery because of classic surgical indications independent of the echocardiographic detection of periannular complications.

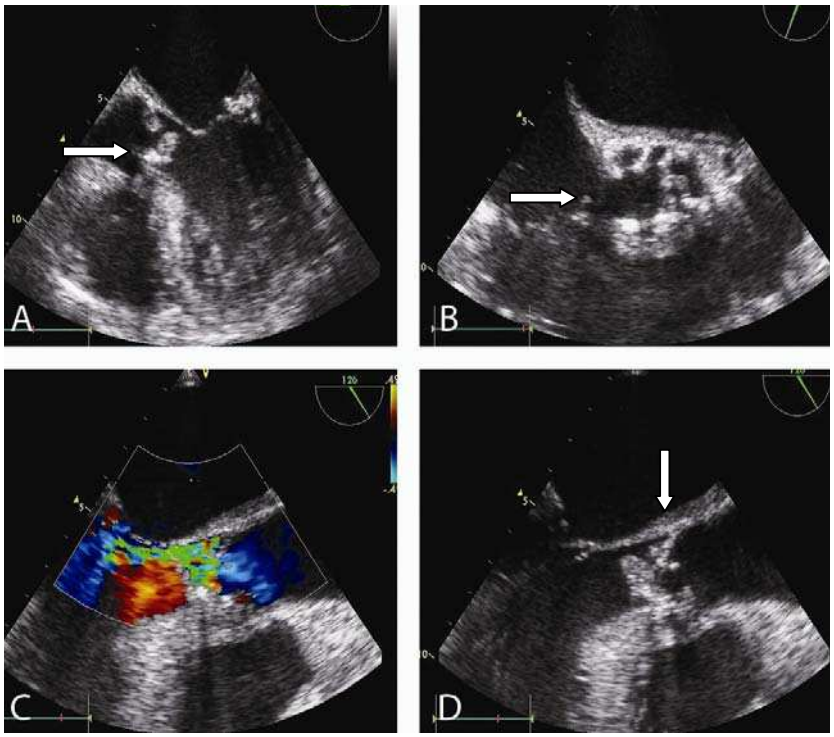


Fig. 1. TEE showing: (A) possible fistula, (B) perforation of the right coronary leaflet, (C) Color flow imaging of the aortic valve showing severe aortic regurgitation due to leaflet perforation, (D) vegetations on the aortic side of the leaflets

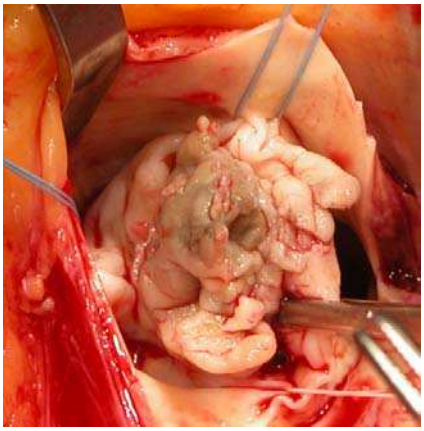

Fig. 2. IE superimposed on severe aortic stenosis with development of small friable vegetations and leaflet abscess

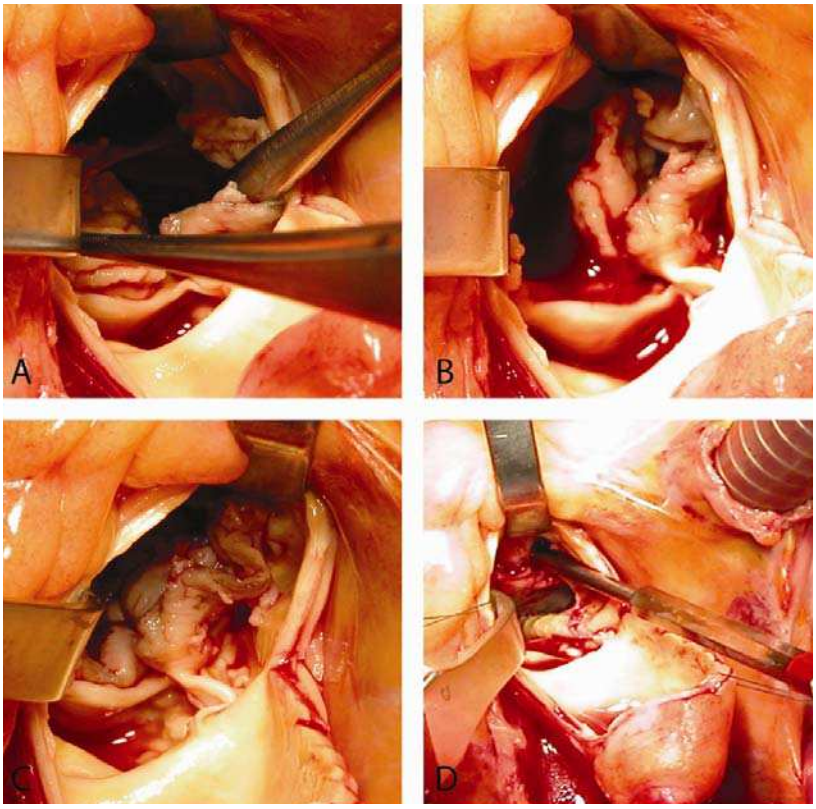


Fig. 3. Complete destruction of the right coronary leaflet (A and B), small vegetations on all leaflets (A, B, C) and ACF to the right ventricle with probe in it (D)

### 3.3 Prosthetic valve endocarditis

PVE is defined as infection occurring in a prosthetic heart valve and has an overall incidence of 0.32% to 1.2% per patient year and cumulative risk of 5% at 10 years (Mahesh et al., 2005). Rates range from 1% to 3% within the first year however the highest rate of infection occurs in the first three postoperative months. By six months, rates stabilize to 0.4% annually (Kwan-Leung & Embli, 2006). Despite advances in diagnosis, medical and surgical therapy over the past few decades, PVE still carries a substantial risk of morbidity, with overall mortality ranging from 20% to 80% of affected patients (Musci et al., 2010). Important factors in the pathogenesis include type of prosthesis, previous native valve endocarditis, male gender, and long cardiopulmonary bypass time. A number of studies have reported a higher incidence of PVE after mechanical valve replacement in comparison with the biologic valve replacement during the initial few months after implantation. Early PVE may develop when pathogens reach the valve prosthesis by way of direct contamination intraoperatively or via hematogenous spread over the initial days and weeks after surgery. The pathogens have direct access to the prosthesis-annulus interface and to perivalvular tissue along suture pathways because the valve sewing ring, cardiac annulus, and anchoring sutures are not endothelialized early after valve implantation. These structures are coated with host proteins such as fibronectin and fibrinogen to which some organisms can adhere to and initiate infection. On the other hand, as the sewing ring, sutures, and adjacent tissues become endothelialized in months after valve replacement, sites for adherence of microorganisms and access to host tissues adjacent to the prosthesis are altered. The pathogenesis of late PVE has been postulated to resemble native valve endocarditis. This temporal classification is based on marked differences in microbiologic causes of early and late PVEs. Early PVE accounts for approximately 30% of all PVE cases and is predominantly caused by *S. aureus*, gram-negative bacilli, and coagulase negative *Staphylococci*. There are also differences in infection localization with regard to type of prosthesis used to replace aortic valve. Infections in mechanical valves generally involve the sewing ring or adherent thrombi, and can lead to paraprosthetic leaks, ring abscesses, and invasive infection, necessitating operative intervention. Bioprostheses are less susceptible to early infection, which is often restricted to the leaflets, making cure with antibiotics more likely but increasing the chances of late failure due to degeneration of the cusps (Mahesh et al., 2005).

Severe heart failure, staphylococcal infection and complicated PVE are designated as markers of both in-hospital and late mortality, while severe heart failure and *S. aureus* infection were the only independent predictors of in-hospital death (Habib et al., 2008). Data from the International Collaboration on Endocarditis showed that in-hospital death, which occurred in 22.8% of the study patients, was predicted by older age, health-care-associated infection, *S. Aureus* infection and complications of PVE, including heart failure, stroke, intra-cardiac abscess and persistent bacteraemia (Wang et al., 2007).

Because the presence of a prosthetic heart valve is a predisposing factor to the development of endocarditis, antibiotic prophylaxis and therapy at the time of health-care-related procedures has been a mainstay of care of the patient with a prosthetic valve (Wang & Bashore, 2009). For this reason, antibiotic prophylaxis is recommended only for patients with prosthetic heart valves prior to dental procedures (highest rate of possible bacteremia as demonstrated in Table 1.), but not before gastrointestinal or genitourinary procedures (Wilson et al., 2008). However, ESC guidelines do recommend antibiotic prophylaxis in the case of gastrointestinal or genitourinary procedures (Horstkotte et al., 2004).

Patients with suspected PVE should be aggressively treated with broad spectrum antibiotics that are effective against wide range of microorganisms especially *staphylococci* and *streptococci*. In further course of the disease, antibiotic regiment should be optimised based on sensitivity of isolated cultures. This therapy should reduce the risk of systemic embolization by shrinking the size of vegetations. Patient should be carefully monitored and further diagnostic procedures should be performed. TEE is of greatest value because it can provide information of existence and extension of infective process to a surrounding tissue. Negative echocardiography finding does not necessarily exclude PVE. After the diagnosis of PVE, repeat-TEE may be highly sensitive and useful to diagnose complications such as prosthetic valve dysfunction (regurgitation or stenosis), resultant changes in ventricular function or dilation, periannular extension of infection (intra-cardiac abscess or fistula formation), or involvement of other valves (Wang & Bashore, 2009). Surgical consultation should be promptly scheduled given that periannular complications occur in more than 50% of patients and may lead to complete aortic root destruction. Radical surgical debridement with a margin of healthy tissue to eradicate intracardiac foci of infection remains the primary aim of surgery for PVE, enabling secure fixation of the new prosthesis, avoiding recurrent or residual infection, periprosthetic leak or dehiscence, or subannular aneurysm formation (Mahesh et al., 2005).

## 4. Clinical management

The diagnosis of IE remains challenging and continues to be dependent on a constellation of infectious symptoms and signs in association with bacteremia, auscultatory evidence of valvular involvement, and signs of large and/or small-vessel peripheral arterial embolization (Kwan-Leung & Embli, 2006). With availability of technologically sophisticated imaging modalities, establishing IE diagnosis should not be very hard in theory. Recognition is the first step in proper management of IE. Rapid diagnosis, early risk stratification, institution of appropriate bactericidal therapy, and prompt recognition and treatment of complications are the key elements toward a good outcome (Wang & Bashore, 2009).

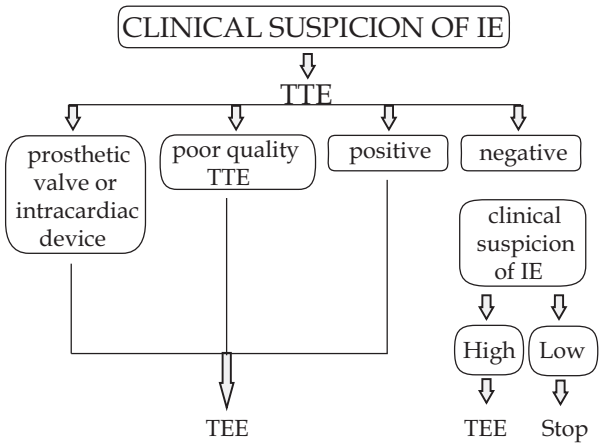


Fig. 4. Indications for initial echocardiography assessment. If initial TEE is negative but suspicion for IE remains, repeat TEE within 7-10 days (Habib et al., 2009)

Diagnosis should be established in regards to clinical presentation and IE diagnostic criteria presented in Table 2., Table 3. and Table 4. Blood cultures remains the single most important investigation in a patient suspected of having IE (*gold standard test*). If appropriate samples are obtained, one could expect to yield growth of the causative organism in over 90% of cases of IE (Kwan-Leung & Embli, 2006). At a minimum, 3 sets of blood cultures should be drawn at least 1h apart prior to antibiotic administration irrespective of body temperature. In most cases, the results of blood cultures would be available within 3 days from the moment they were obtained.

Broad-spectrum parenteral antibiotic therapy should be commenced immediately upon suspicion of IE but after the acquisition of blood cultures. Antibiotic therapy should not be delayed (i.e. should be started even if the blood cultures are not drawn) only when dealing with septic patients with suspected IE. Therapy should be adjusted according to blood culture findings. It should continue for 4-6 weeks so as to eradicate all the pathogens from phagocytic cells and inaccessible vegetations. The precise antibiotic regiment for specific pathogens is presented in detail within the European Society of Cardiology recommendations (Horstkotte et al., 2004). The patient should be evaluated for the signs of immunodepression, malnutrition, or other systemic diseases as these conditions may impair the treatment course and promote development of complications. Additionally, renal function should also be carefully monitored, and due consideration given to probiotic supplements.

Further clinical investigation should be performed using echocardiography and other diagnostic procedures guided by the clinical presentation. As stated earlier, TEE is preferred over TTE because of higher sensitivity and specificity, but TTE may serve as an initial screening test. If echocardiography remains negative but suspicion remains, echocardiography should be repeated within one week. A repeatedly negative study will near-exclude the diagnosis.

Upon completion of the antibiotic regiment, or in the onset of complications or severe hemodynamic deterioration, the patient should be presented to cardiac surgeon to evaluate necessity for the operative intervention and its timing. Table 6 summarizes conditions considered as indications for surgical intervention.

### 4.1 Surgical therapy

Despite many advances in diagnosis and antibiotic therapy of IE, eradication of the septic focus and abolition of the accompanying systemic manifestations usually require some kind of surgical intervention. Surgically demanding cases are those of active IE affecting entire aortic root with development of local periannular complications. Main challenge with acute IE is to address the two coexisting aspects of the disease: the infectious process necessitating removal of all infected tissues to prevent recurrence, and altered valvular anatomy and function to be corrected and restored (Kwan-Leung & Embli, 2006). With regard to the complex pathology, the mortality and morbidity rates associated with surgical therapy remain relatively high - between 3.8 and 22% (d'Udekem et al., 1997). For the purpose of unifying criteria, hospital mortality is considered to be related to the operation when death occurs in the operating room or during the first 30 days after surgery, but also when the patient dies in hospital beyond 30 days without being discharged (Edmunds et al., 1996). There are many factors that may influence surgical mortality in IE giving cause to a risk stratification scoring system.

| Indication | Evidence |
|---|---|
| Emergency indication for cardiac surgery (same day) | |
| Acute AR with early closure of mitral valve | A |
| Rupture of a sinus Valsalva aneurysm into a right heart chamber | A |
| Rupture into the pericardium | A |
| Urgent indication for cardiac surgery (within 1–2 days) | |
| Valvular obstruction | A |
| Unstable prosthesis | A |
| Acute AR or MR with heart failure, NYHA III–IV | A |
| Septal perforation | A |
| Evidence of annular or aortic abscess, sinus or aortic true or false aneurysm, fistula formation, or new onset conduction disturbances | A |
| Major embolism + mobile vegetation >10mm + appropriate antibiotic treatment < 7–10 days | B |
| Mobile vegetation > 15mm + appropriate antibiotic therapy < 7–10 days | C |
| No effective antimicrobial treatment available | A |
| Elective indication for cardiac surgery (earlier is usually better) | |
| Staphylococcal prosthetic valve infective endocarditis | B |
| Early prosthetic valve infective endocarditis (≤2 months after surgery) | B |
| Evidence of progressive paravalvar prosthetic leak | A |
| Evidence of valve dysfunction and persistent infection after 7–10 days of appropriate antibiotic treatment, as indicated by presence of fever or bacteremia, provided there are no noncardiac causes for infection | A |
| Fungal infective endocarditis caused by a mould | A |
| Fungal infective endocarditis caused by a yeast | B |
| Infection with difficult-to-treat organisms | B |
| Vegetation growing larger during antibiotic treatment > 7 days | C |

*A: Strong evidence or general agreement that cardiac surgery is useful and effective; B: Inconclusive or conflicting evidence or a divergence of opinion about the usefulness or efficacy of cardiac surgery but with weight of evidence & opinion of the majority being in favour; C: Inconclusive or conflicting evidence or divergence of opinion; lack of clear consensus on the basis of evidence or opinion of the majority.*
*AR - aortic regurgitation; MR - mitral regurgitation; NYHA - New York Heart Association functional class.*

Table 6. Indications for surgical intervention in patients with IE (adapted from Delahaye et al., 2004)

As shown in Table 6., indication for surgical intervention is usually based on development of heart failure that cannot be managed otherwise, signs of uncontrolled infection despite aggressive medical therapy, and manifestation or increased risk of embolization. These surgical indications stand for both native valve endocarditis and PVE. Prior to establishing an indication, surgeon must become aware of all the compromising factors that may affect the outcome of the surgery: phase of the infective process (acute or active phase is associated

with higher mortality), structural and functional status of afflicted valve, comorbidites). In patients with high risk of coronary heart disease, preoperative coronarography should be performed to assess the necessity of coronary artery bypass grafting in the same act.
Knowing that cardiac surgery is an integral part of IE treatment strategy, it is advisable that cardiac surgery team should be included in patient evaluation following IE diagnosis. This will both enable the surgical team to become fully familiar with the patient case as the surgery is eventually called for, but also work with the medical team to determine the need and optimum timing for surgery (Kwan-Leung & Embli, 2006).

### 4.1.1 Timing of surgery

Surgical treatment is used in approximately half of patients with IE because of severe complications (Habib et al., 2009). The right timing of an operation is absolutely essential for success. The patient status has to be optimized to the maximum capacity in order to achieve maximal benefit from the operation. Operating too soon carries a higher risk of a failure due to unstable patient condition, specific cardiac tissue condition (friability) which may lead to embolization and peri-prosthetic leakage, and greater possibility of recurrence. On the other hand, waiting too long for the operative treatment may lead to a life-threating systemic infection (septic state) with development of multiple organ dysfunction syndrome, or extensive structural destruction of the heart valves and surrounding tissues. Surgical timing strategies have evolved significantly over the previous years, owing to the developments in the medical management and diagnostic tools, but despite this advent, when-to-operate still remains a controversial issue.
In some cases surgery needs to be performed on an emergency (within 24 hours) or urgent (within a few days) basis irrespective of the duration of antibiotic treatment. In other cases surgery can be postponed to allow 1 or 2 weeks of antibiotic treatment under careful clinical and echocardiographic observation before an elective surgical procedure is carried out. Early surgical treatment is justified in patients with high-risk features that make unlikely the possibility of cure with antibiotic treatment, unless they also have co-morbid conditions or complications that make the prospect of recovery remote.
According to European Society of Cardiology Guidelines (Habib et al., 2009), unless severe co-morbidity exists, early surgery is recommended in the following cases: the presence of heart failure, or presence of locally uncontrolled infection in the cases of native valve IE. The decision to operate-on early to prevent embolism is always difficult and specific for every patient. Governing factors include size and mobility of the vegetation, previous embolism, type of microorganism, and duration of antibiotic therapy.

### 4.1.2 Types of surgical management

During the preoperative evaluation and clinical management a surgeon is presented with a variety of information to evaluate and make an indication for surgical intervention. Exactly what type of intervention is going to be needed will be unclear until the moment the aortic root is open inside the operative theatre. No matter how accurate the pre-operative diagnostics, intra-operative finding will ultimately guide the ongoing operation.
The basic principles of operative treatment are: to remove all destroyed tissue, to resolve local complications if any, and to anatomically reconstruct the valve if it's possible or to replace it entirely. It is evident that the exclusive involvement of the leaflets makes it easier to perform surgical intervention with limited technical difficulty. The problem arises when infection spreads beyond the native annulus.

Aortic valve replacement (AVR) is the cornerstone operation in setting of aortic valve IE. When repair is an option it is preferred over the replacement, although feasibility of aortic valve repair is reduced with prevalence of extensive tissue destruction in an aortic IE setting (Kwan-Leung & Embli, 2006). Vegetectomy, a novel technique, has also been introduced in common practice (Chen et al., 2009). This repair technique may be considered in cases of limited vegetation presence and without severe leaflet involvement or extension into periannular tissue. Vegetations should not be large in size nor abundantly present because the consequent vegetectomy would impair the coaptation process of the valve. Antiobiotic therapy before the operation should be aggressive to eliminate the presence of pathogens and to reduce the chance of recurrence.

Several recent studies evaluated outcome after replacement devices were used, that is, biological or mechanical valves. The results were generally favourable and have noted no significant difference in mortality between the two valve types. The choice of valve type is to surgeon's preference and according to generally accepted indications for AVR. Mechanical valves are charcterized as reliable and durable but require lifelong anticoagulation (taken orally). Bioprosthesis are limited by their durability of 10-15 years but do not require oral anticoagulation therapy. Surgeon needs to be aware of all factors that may influence the choice of valve such as patient age, germinative period, risk of haemorrhage or thrombosis following oral antiocoagulation therapy compliance and so forth. There is no significant difference in either short-term or long-term survival between mechanical and bioprosthetic valves.

In the case of severe aortic root involvement with severe damage of aortic valve and surrounding tissue, a composite graft incorporating a prosthetic valve and a vascular tube graft can be used. If more than 50% of the aortic annulus has been destroyed, homograft (allograft) root replacement may be the treatment of choice. These are the most serious conditions that can be seen in aortic root as a consequence of IE. Aortic homograft represent the ideal tissue to reconstruct the complicated aortic root as they allow for a radical treatment by eliminating abscesses, closing fistulae, the associated treatment of the sinotubular junction and ascending aorta, and the implantation of a biological device that does not require anticoagulation and is resistant to infection (Mestres et al., 1993). Although no conclusive data is available comparing homografts and prosthetic valves with respect to durability and risk of recurrent IE, current data from surgical series indicate satisfactory results with the use of homografts (Riberi et al., 1997). Another indication for use of homograft is PVE which represents a difficult operation with need of extensive removal of necrotic tissue and debris (Sabik et al., 2002). A recent study compared 5-year survival rate for different valve implant types. It demonstrated that the survival is comparable for mechanical valves and homografts, but is significantly lower for bioprosthesis (Nguyen et al., 2010). Another research group also investigated relationship between mechanical valves and homografts in native valve endocarditis establishing advantage of mechanical prosthesis over homografts (Klieverik et al., 2009).

Stentless aortic valves may also be used for AVR in the case of IE (Perrotta & Lentini, 2010). Stentless Aortic Valve Conduit in patients with native or prosthetic aortic valve endocarditis appears to demonstrate good results, similar to those of cryopreserved homografts. Study comparing two groups of patients treated with stentless valves and homografts, demonstrating an equal reinfection rate of 4% and lower mortality for the stentless group (12% vs. 16%, respectively). The reinfection rate is found to be lower for the homograft and stentless groups than for the patients treated with standard prostheses, respectively, 5.8%,

3.7% and 33%. The stentless valve offers a reinfection rate and postoperative echocardiographic data comparable to those achieved with homografts (Siniawski et al., 2003).

| Study | Conduit/ prosthesis | No. of pts | Peri-annular aortic root abscess (%) | Op. mortality (%) | Freedom from recurrent infection (follow-up duration) | Freedom from reop. (follow-up) | Survival rate (%) (follow-up) |
|---|---|---|---|---|---|---|---|
| Yankah et al. (2005) | Homograft in NVE | 161 | 100 | 9.3 | 91% (10 years) | 82.9% (17 years) | 87 (11 years) |
| Sabik et al. (2002) | Homograft in PVE | 103 | 78 | 3.9 | 95% (10 years) | - | 73 (5 years) 56 (10 years) |
| Siniawski et al. (2005) | Shelhigh noreact stentless prosthesis | 75 | 100 | 12 (60 days) | 96% (17±10 months) | - | |
| | Homograft | 68 | 100 | 16 (60 days) | 96% (17±10 months) | | |
| Kon et al. (2002) | Stentless porcine aortic root bioprosthesis | 104 | - | 3.9 | 96.9% (8 years) | 100 (8 years) | 59.8 (8 years) |
| Schmidtke et al. (2007) | Ross procedure | 296 | - | 0.3 | 0 (47.3 ± 28.6 months) | - | 99.7 (47.3 ± 28.6 months) |
| Avierinos et al. (2007) | Homograft | 54 | 63 | 9 | 44 ± 10% (10 years survival-free from the combined endpoint, including recurrence IE, prosthesis dysfunctions and long-term cardiovascular mortality) | | |
| | Convent. prosthesis | 73 | - | - | | | |

Table 7. Comparision of multiple conduits for periannular extension of aortic valve endocarditis (reproduced with permission from Kang et al., 2009)

Another suggested procedure that may be used in the setting of IE is the Ross procedure (Joyce et al., 1994). The Ross procedure consists of autotransplantation of the pulmonary valve. Studies reporting reproducible results following the Ross procedure in the treatment of IE have not yet been published in quantity that would allow comparison with other available approaches. In the setting of PVE, the Ross procedure should be introduced for further improvement of surgical results (Ishikawa et al., 2009).

Short-term and long-term results following operation due to IE are generally satisfactory. There is however a statistical difference in survival among patients with native valve IE and PVE. One year survival in native valve endocarditis is reported to be from 91% to 93%, while in PVE 79,7%. Five year survival in native valve IE ranges between 54% and 93%, and for PVE it is 64,2%. Ten year survival for native valve IE is reported to be from 54% to 67,5%, and for PVE from 33.5% to 58% (Kwan-Leung & Embli, 2006).

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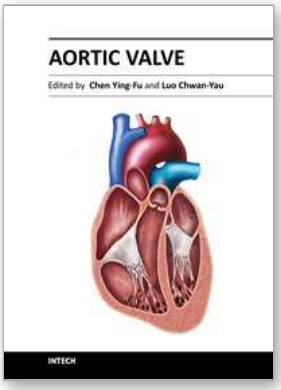


**Aortic Valve**

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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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