University of Diyala

Collage of Medicine

sixth stage

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Infective Endocarditis

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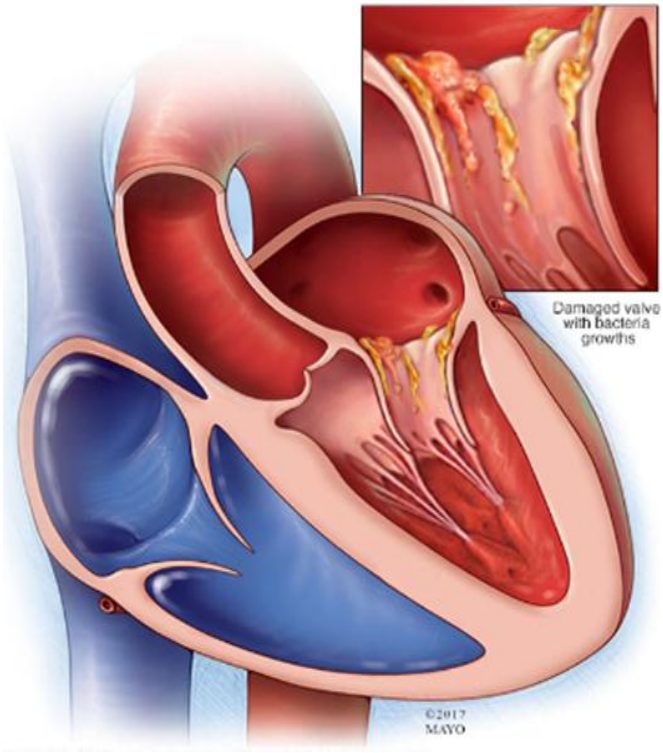
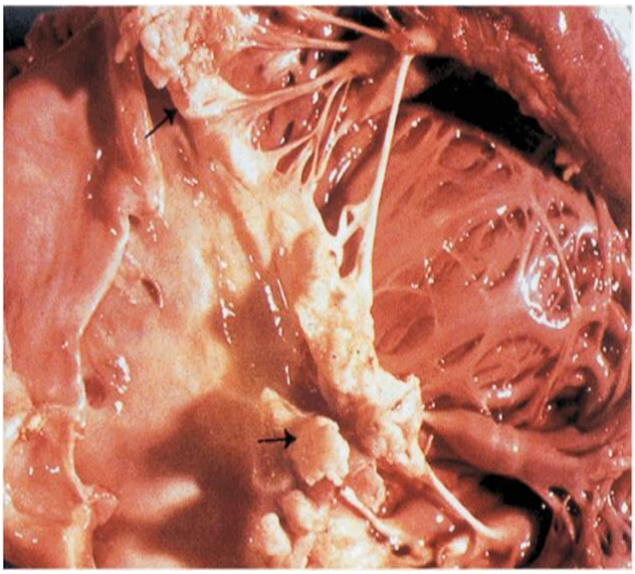


On this lecture we going to discuss the following:

- *What infective endocarditis mean? And what are its types?*
- *What are the most causative agents?*
- *The mechanism of pathogenesis and how can it develop?*
- *What manifestations can this disease show?*
- *The definitive diagnosis of infective endocarditis*
- *What investigations we have to do?*
- *How infective endocarditis can be managed and treated?*
- *What cardiac and extracardiac complications can infective endocarditis cause?*
- *Differential diagnosis of infective endocarditis.*
- *The outcome of infective endocarditis and how can be prevented.*

Introduction

Infective endocarditis is caused by microbial infection of a heart valve, the lining of a cardiac chamber or blood vessel, or by a congenital anomaly. Both native and prosthetic valves can be affected. The most common causes of infective endocarditis are streptococci and staphylococci but other organisms may also be involved. **(1)**



The prototypic lesion of infective endocarditis, the vegetation, is a mass of platelets, fibrin, microorganisms, and scant inflammatory cells. Infection most commonly involves heart valves but may also occur on the low-pressure side of a ventricular septal defect, on mural endocardium damaged by aberrant jets of blood or foreign bodies, or on intracardiac devices themselves. The analogous process involving arteriovenous shunts, arterio-arterial shunts (patent ductus arteriosus), or a coarctation of the aorta is called infective endarteritis.
Endocarditis can be classified according to the temporal evolution of disease, the site of infection, the cause of infection, or the predisposing risk factor (e.g., injection drug use, association with health care). ***Acute*** endocarditis is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites, and, if untreated, progresses to death within weeks. ***Subacute*** endocarditis follows an indolent course; causes structural cardiac damage only slowly, if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm. **(2)**

- *Strict case definitions were applied to 123 clinically diagnosed cases of IE. Cases were categorized as definite 19, probable 44, or possible 41 endocarditis or were rejected 19. Compared to other published studies, our patients had an advanced mean age 57, high incidence of underlying valvular disease 66%, short mean duration of symptoms 27 days, and 15% mortality. Deaths were caused by heart failure, neurologic events, or superinfection.* **(3)**

Epidemiology

The incidence of infective endocarditis in community-based studies ranges from 5 to 15 cases per 100 000 per annum. More than 50% of patients are over 60 years of age. In a large British study, the underlying condition was rheumatic heart disease in 24% of patients, congenital heart disease in 19%, and other cardiac abnormalities such as calcified aortic valve or floppy mitral valve in 25%. The remaining 32% were not thought to have a pre-existing cardiac abnormality. Bacterial endocarditis is a serious illness; the case fatality is approximately 20% even with treatment, and is even higher in those with prosthetic valve endocarditis and those infected with antibiotic-resistant organisms. **(1)**

- *Important changes occurred in IE epidemiology over the last half-century, especially in the last decade. Staphylococcal and enterococcal IE percentage increased while SV and CN IE decreased. Moreover, mean age at diagnosis increased together with male: female ratio. These changes should be considered at the time of decision-making in treatment and prophylaxis for IE.* **(4)**

Etiology

Native valve endocarditis

- Rheumatic valvular disease (30% of NVE)
- Congenital heart disease (15% of NVE)
- arteriosus, ventricular septal defect, tetralogy of
- Fallot, or any native or surgical high-flow lesion.
- Mitral valve prolapse with an associated murmur (20% of NVE)

Prosthetic valve endocarditis

Early PVE caused by S aureus and S epidermidis. These nosocomially acquired organisms are often methicillin-resistant. Late disease is most commonly caused by streptococci. Overall, CoNS are the most frequent cause of PVE (30%).

Intravenous Drug Abuse infective endocarditis

S aureus is the most common (< 50% of cases) etiologic organism in patients with IVDA IE. Groups A, C, and G streptococci and enterococci are also recovered from patients with IVDA infective endocarditis.

Nosocomial/healthcare-associated infective endocarditis

This caused by organisms belong to underlying bacteremia. The gram-positive cocci (ie, S aureus, CoNS, enterococci) are the most common pathogens.

Fungal endocarditis

Candida and Aspergillus species are the two most common etiologic fungi. Fungal endocarditis is found in intravenous drug users and intensive care unit patients who receive broad-spectrum antibiotics. **(12)**

Pathophysiology

Infective endocarditis typically occurs at sites of pre-existing endocardial damage, but infection with particularly aggressive organisms such as Staphylococcus aureus can cause endocarditis in a previously normal heart. Staphylococcal endocarditis of the tricuspid valve is a common complication of intravenous drug use. Many acquired and congenital cardiac lesions are vulnerable, particularly areas of endocardial damage caused by a high-pressure jet of blood, such as ventricular septal defect, mitral regurgitation, many of which are haemodynamically insignificant. In contrast, the risk of endocarditis at the site of haemodynamically important low-pressure lesions, such as a large atrial septal defect, is minimal. Infection tends to occur at sites of endothelial damage because they attract deposits of platelets and fibrin that are vulnerable to colonization by blood-borne organisms. The avascular valve tissue and presence of fibrin and platelet aggregates help to protect proliferating organisms from host defense mechanisms.

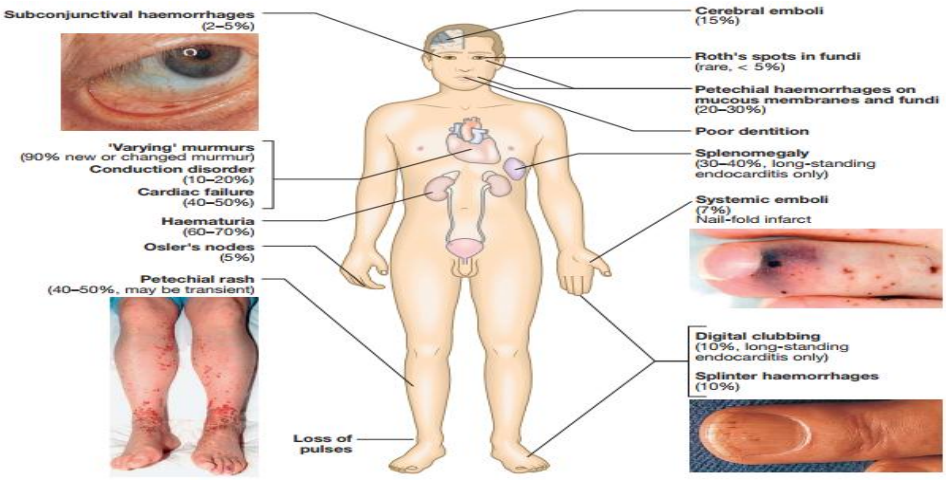
When the infection is established, vegetations grow and may become large enough to cause obstruction or embolism. Adjacent tissues are destroyed and abscesses may form. Valve regurgitation may develop or increase if the affected valve is damaged by tissue distortion, cusp perforation or disruption of chordae. Extracardiac manifestations, such as vasculitis and skin lesions, may occur as the result of either emboli or immune complex deposition. In fatal cases, infarction of the spleen and kidneys and, sometimes, an immune glomerulonephritis may be found at postmortem. **(1)**

- *Endocarditis pathogens colonize valves with pre-existing sterile vegetations or valves with minimal endothelial lesions. Inflamed endothelia produce cytokines, integrins, and tissue factor, which in turn attract fibronectin, monocytes, and platelets. Bacteria attaching to such structures further activate the cascade, becoming embedded and protected from host defenses.* **(5)**

Clinical feature

Subacute endocarditis

This should be suspected when a patient with congenital or valvular heart disease develops a persistent fever, unusual tiredness, night sweats or weight loss, or develops new signs of valve dysfunction or heart failure. Other features include purpura and petechial haemorrhages in the skin and mucous membranes, splinter haemorrhages under the fingernails or toenails. Osler's nodes are painful, tender swellings at the fingertips that are probably the product of vasculitis; they are rare. Digital clubbing is a late sign. The spleen is frequently palpable; in *Coxiella* infection, the spleen and liver may be enlarged. Non-visible haematuria is common.



Acute endocarditis

This presents as a severe febrile illness with prominent and changing heart murmurs and petechiae. Embolic events are common, and cardiac or renal failure may develop rapidly. Abscesses may be detected on ECG. Partially treated acute EI behaves like subacute EI.

Post-operative endocarditis

This may present as an unexplained fever in a patient who has had heart valve surgery. The infection usually involves the valve ring and may resemble subacute or acute endocarditis, depending on the virulence of the organism. (1)

- *Clinical manifestations of infective endocarditis may involve almost all body organs. They are classified as either cardiac or extra-cardiac manifestation. The first stage of infection is the development of intra-cardiac vegetation, which may further spread with an increase in size and number of vegetations.* **(6)**

Diagnosis

Definitive diagnosis is generally made by using the Duke criteria. Patients with two major, or one major and three minor, or five minor have definite endocarditis. Patients with one major and one minor, or three minor have possible IE. **(1)**

Major criteria
Positive blood culture • **Typical organism from two cultures** • **Persistent positive blood cultures taken >12 hrs apart** • **Three or more positive cultures taken over >1 hr** **Endocardial involvement** • **Positive echocardiographic findings of vegetations** • **New valvular regurgitation**
Minor criteria
• **Predisposing valvular or cardiac abnormality** • **Intravenous drug misuse** • **Pyrexia ≥38°C** • **Embolic phenomenon** • **Vasculitic phenomenon** • **Blood cultures suggestive: organism grown but not achieving major criteria** • **Suggestive echocardiographic findings**

- *Patients with prosthetic valve and intra-cardiac device–related endocarditis are being seen more and this condition difficult to diagnose with conventional microbiological and imaging techniques. The modified Duke criteria lack sensitivity in this group and should be supplemented with newer imaging techniques, including 18F-fluorodeoxyglucose positron emission tomography (18F-FDG-PET) and single-photon emission computed tomography.* **(7)**

Investigation

Blood Cultures

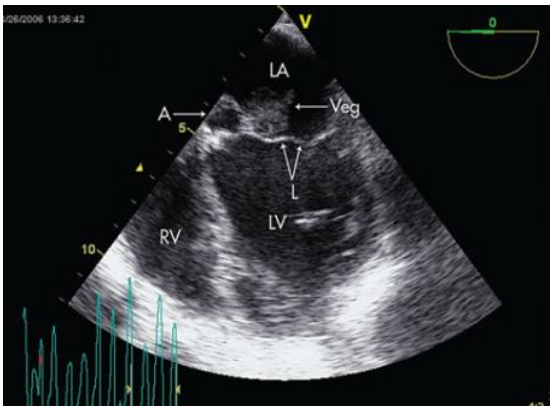
is the pivotal investigation to identify the organism that cause the infection and to guide antibiotic therapy. Three to six sets of blood cultures should be taken prior to commencing therapy and should not wait for episodes of pyrexia. The first two specimens will detect bacteraemia in 90% of culture-positive cases. A meticulous aseptic technique is essential. Taking discrete sets of blood cultures from peripheral sites at intervals of ≥ 6 hours reduces the risk of misdiagnosis due to contamination with skin commensals. **(1)**

Non-Blood-Culture Tests

Serologic tests can be used to implicate organisms that are difficult to recover by blood culture: Brucella, Bartonella, Legionella, Chlamydia psittaci, and C. burnetii. In vegetations recovered at surgery or by embolectomy, pathogens can also be identified by culture; by microscopic examination with special stains; and by polymerase chain reaction (PCR) recovery of microbial DNA or DNA encoding the 16S or 28S ribosomal unit (16S rRNA or 28S rRNA), which when sequenced allows identification of bacteria and fungi, respectively. **(2)**

Echocardiography

is key for detecting and following the progress of vegetations, for assessing valve damage and for detecting abscess formation. Vegetations as small as 2–4 mm can be detected by transthoracic echocardiography, and even smaller ones (1–1.5 mm) can be visualized by trans-oesophageal echocardiography (TOE). the sensitivity of transthoracic echo is approximately 65% but that of TOE is more than 90%. Failure to detect vegetations does not exclude the diagnosis. **(1)**



Management

- ✓ Any source of infection should be removed as soon as possible; for example, a tooth with an apical abscess should be extracted. Empirical treatment depends on the mode of presentation, the suspected organism and the presence of a prosthetic valve or penicillin allergy.
- ✓ If the presentation is subacute, antibiotic treatment should ideally be withheld until the results of blood cultures are available. However, if empirical antibiotic treatment is considered necessary, amoxicillin (2 g 6 times daily IV) should be considered (with or without gentamicin).
- ✓ If the presentation is acute, empirical therapy should be started with vancomycin (1 g twice daily IV) and gentamicin (1 mg/kg twice daily IV), with dose adjustment based on antibiotic levels.
- ✓ Patients with suspected prosthetic valve endocarditis should be treated with vancomycin and gentamicin at the above-mentioned doses, plus rifampicin orally

in a dose of 300–600 mg twice daily. Following identification of the causal organism, determination of the minimum inhibitory concentration (MIC) for the organism helps guide antibiotic therapy.

- ✓ A 2-week treatment regimen may be sufficient for fully sensitive strains of streptococci, provided specific conditions are met.
- ✓ Cardiac surgery with debridement of infected material and valve replacement may required in a substantial proportion of patients, particularly those with *Staph aureus* and fungal infections. Antimicrobial therapy must be started before surgery**.**

Indications for cardiac surgery are:

- Heart failure due to valve damage.
- Failure of antibiotic therapy (persistent/uncontrolled infection).
- Large vegetations on left-sided heart valves with echo appearance
- suggesting high risk of emboli
- Previous evidence of systemic emboli
- Abscess formation. **(1)**

16.96 Antimicrobial treatment of common causative organisms in infective endocarditis

Antimicrobial susceptibility	Antimicrobial	Dose	Duration	
			Native valve	Prosthetic valve
Streptococci				
Penicillin MIC ≤0.125 mg/L	Benzylpenicillin IV	1.2 g 6 times daily	4 weeks[1]	6 weeks
Penicillin MIC >0.125, ≤0.5 mg/L	Benzylpenicillin IV and gentamicin IV	2.4 g 6 times daily 1 mg/kg twice daily[2]	4 weeks 2 weeks	6 weeks 2 weeks
Penicillin MIC >0.5 mg/L	Vancomycin IV and gentamicin IV	1 g twice daily[3] 1 mg/kg twice daily[2]	4 weeks 4 weeks	6 weeks 6 weeks
Enterococci				
Amoxicillin MIC ≤4 mg/L and gentamicin MIC ≤128 mg/L	Amoxicillin IV and gentamicin IV[2]	2 g 6 times daily 1 mg/kg twice daily[2]	4 weeks 4 weeks	6 weeks 6 weeks
Amoxicillin MIC >4 mg/L and gentamicin MIC ≤128 mg/L	Vancomycin IV and gentamicin IV[2]	1 g twice daily[3] 1 mg/kg twice daily[2]	4 weeks 4 weeks	6 weeks 6 weeks
Staphylococci – native valve				
Meticillin-sensitive	Flucloxacillin IV	2 g 4–6 times daily[4]	4 weeks	–
Meticillin-resistant, vancomycin MIC ≤2 mg/L, rifampicin-sensitive	Vancomycin IV Rifampicin orally	1 g twice daily[3] 300–600 mg twice daily	4 weeks 4 weeks	– –
Staphylococci – prosthetic valve				
Meticillin-sensitive	Flucloxacillin IV and gentamicin IV and rifampicin orally	2 g 4–6 times daily 1 mg/kg twice daily[2] 300–600 mg twice daily	– – –	6 weeks 6 weeks 6 weeks
Meticillin-resistant, vancomycin MIC ≤2 mg/L, rifampicin-sensitive	Vancomycin IV and rifampicin orally	1 g twice daily[3] 300–600 mg twice daily	– –	6 weeks 6 weeks

Prophylactic antibiotics weren't given before infective endocarditis to 8/11 cardiac patients at risk and who underwent an at risk procedure. Among the 55 cardiac patients at risk and with fever and who consulted a physician, blood cultures were not performed before antibiotic therapy was initiated for 32 patients. In-hospital antibiotic therapy was incorrect for 23 patients. **(8)**

Deferential diagnosis

- Thrombotic nonbacterial endocarditis
- Vasculitis, Temporal arteritis
- Marantic endocarditis
- Septic pulmonary infarction
- Tricuspid regurgitation
- Antiphospholipid Syndrome
- Atrial Myxoma
- Physical Medicine and Rehabilitation for Systemic Lupus Erythematosus
- Polymyalgia Rheumatica
- Primary Cardiac Neoplasms
- Reactive Arthritis
- Lyme disease.
- Fever of unknown origin (FUO). **(12)**

Prognosis

Endocarditis is a heterogeneous disease that occurs in extremely heterogeneous patient populations. Many factors can adversely affect outcome; these include older age, severe comorbid conditions and diabetes, delayed diagnosis, involvement of prosthetic valves or the aortic valve, an invasive (S. aureus) or antibiotic-resistant (P. aeruginosa, yeast) pathogen, intracardiac and major neurologic complications, and an association of infection with health care. Death or poor outcome often is related not to failure of antibiotic therapy but rather to the interactions of comorbidities and endocarditis-related end-organ complications. **(2)**

- *Despite improvements in medical and surgical therapies, infective endocarditis is associated with poor prognosis and remains a therapeutic challenge. Many factors affect the outcome of this serious disease, including virulence of the microorganism and characteristics of the patients.* **(9)**

- *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.* **(10)**

Complication

Extracardiac Complications are Splenic abscess develops in 3–5% of patients with endocarditis. Effective therapy requires either image-guided percutaneous drainage or splenectomy. Mycotic aneurysms occur in 2–15% of endocarditis patients; one-half of these cases involve the cerebral arteries and present as headaches, focal neurologic symptoms, or hemorrhage. Cerebral aneurysms should be monitored by angiography. Some will resolve with effective antimicrobial therapy, but those that persist, enlarge, or leak should be treated surgically if possible. Extracerebral aneurysms present as local pain, a mass, local ischemia, or bleeding; these aneurysms are treated surgically. **(2)**

- *Complications of IE may involve cardiac structures when the infection spreads within the heart, or extra cardiac ones when the cause is usually from embolic origin; they may also be due to medical treatment or to the septic condition itself. A variety of complications may occur in most of patients. Congestive heart failure (CHF) is the most important complication of IE, which has the greatest impact on prognosis. Periannular abscesses are a relatively common complication of IE (42% to 85% of cases during surgery or at autopsy respectively), associated with a higher morbidity and mortality. Systemic embolization occurs in 22% to 50% of cases; emboli may involve major arteries, mostly affecting the central nervous system.* **(11)**

Prevention

Until recently, antibiotic prophylaxis was routinely given to people at risk of infective endocarditis undergoing interventional procedures. However, as this has not been proven to be effective and the link between episodes of infective endocarditis and interventional procedures has not been demonstrated, antibiotic prophylaxis is no longer offered routinely. **(1)**

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