Infective Endocarditis

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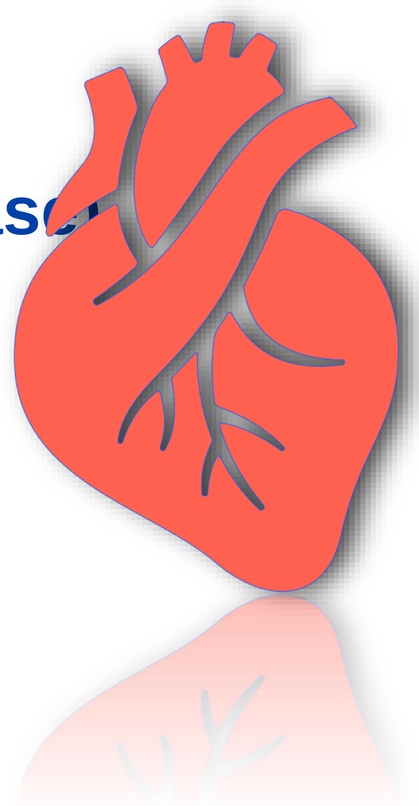

- This is caused by microbial infection of a heart valve, the lining of a cardiac chamber or blood vessel, or a congenital anomaly. Both native and prosthetic valves can be affected. The most common causes of infective endocarditis are streptococci and staphylococci but other organisms may also be involved.

- **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.

- **Pathophysiology**

- Infective endocarditis typically occurs at sites of pre-existing endocardial damage, but infection with particularly virulent or 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 and aortic 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 colonisation by blood-borne organisms. The avascular valve tissue and presence of fibrin and platelet aggregates help to protect proliferating organisms from host defence mechanisms. When the infection is established, vegetations composed of organisms, fibrin and platelets 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. Mycotic aneurysms may develop in arteries at the site of infected emboli. In fatal cases, infarction of the spleen and kidneys and, sometimes, an immune glomerulonephritis may be found at postmortem.

- **Microbiology**

- Over three-quarters of cases are caused by streptococci or staphylococci. Viridans streptococci, such as Streptococcus mitis and Strep.

- sanguis, which are commensals in the oral cavity, can enter the blood stream on chewing or tooth-brushing, or at the time of dental treatment, and are common causes of subacute endocarditis . Other organisms, including Enterococcus faecalis, E. faecium and Strep. gallolyticus subsp. gallolyticus (previously known as Strep. bovis), may enter the blood from the bowel or urinary tract. Patients who are found to have endocarditis caused by Strep. gallolyticus should undergo colonoscopy, since this organism is associated with large-bowel malignancy.

- Staph. aureus has now overtaken streptococci as the most common cause of acute endocarditis. It originates from skin infections, abscesses or vascular access sites such as intravenous and central lines, or from intravenous drug use. It is highly virulent and invasive, usually producing florid vegetations, rapid valve destruction and abscess formation. Other causes of acute endocarditis include Strep. pneumoniae and Strep. pyogenes Post-operative endocarditis after cardiac surgery may affect native or prosthetic heart valves or other prosthetic materials. The most common organisms are coagulase-negative staphylococci such as Staph. epidermidis, which are part of the normal skin flora.

- There is frequently a history of wound infection with the same organism. Coagulase-negative staphylococci cause native valve endocarditis in approximately 5% of cases and this possibility should always be considered before they are dismissed as blood culture contaminants. Another coagulase-negative staphylococcus, Staph. lugdenensis, causes a rapidly destructive acute endocarditis that is associated with previously normal valves and multiple emboli. Unless accurately identified, it may also be overlooked as a contaminant.

- In Q fever endocarditis due to Coxiella burnetii, the patient often has a history of contact with farm animals. The aortic valve is usually affected and there may also be hepatitis, pneumonia and purpura. Life-long antibiotic therapy may be required. In about 3%–4% of cases, endocarditis may be caused by Gramnegative bacteria of the so-called HACEK group (Haemophilus aphrophilus – now known as Aggregatibacter aphrophilusAggregatibacter actinomycetemcomitans; Cardiobacterium hominis; Eikenella corrodens; and Kingella kingae). These are slow-growing, fastidious Gram-negative organisms that are oropharyngeal commensals. The diagnosis may be revealed only after prolonged culture and the organisms may be resistant to penicillin.

- Brucella endocarditis is associated with a history of contact with goats or cattle and often affects the aortic valve.

- Yeasts and fungi, such as Candida and Aspergillus, may attack previously normal or prosthetic valves, particularly in immunocompromised patients or those with in-dwelling intravenous catheters. Abscesses and emboli are common, therapy is difficult, surgery is often required and mortality is high. Concomitant bacterial infection may be present.

16.93 Endocarditis in old age

- **Symptoms and signs**: may be non-specific, with delirium, weight loss, malaise and weakness, and the diagnosis may not be suspected.
- **Common causative organisms**: often enterococci (from the urinary tract) and *Streptococcus gallolyticus* subsp. *gallolyticus* (from a colonic source).
- **Morbidity and mortality**: much higher.

16.94 Microbiology of infective endocarditis

Pathogen	Of native valve (n = 280)	In injection drug users (n = 87)	Of prosthetic valve	
			Early (n = 15)	Late (n = 72)
Staphylococci	124 (44%)	60 (69%)	10 (67%)	33 (46%)
Staph. aureus	106 (38%)	60 (69%)	3 (20%)	15 (21%)
Coagulase-negative	18 (6%)	0	7 (47%)	18 (25%)
Streptococci	86 (31%)	7 (8%)	0	25 (35%)
Oral	59 (21%)	3 (3%)	0	19 (26%)
Others (non-enterococcal)	27 (10%)	4 (5%)	0	6 (8%)
***Enterococcus* spp.**	21 (8%)	2 (2%)	1 (7%)	5 (7%)
HACEK	12 (4%)	0	0	1 (1%)
Polymicrobial	6 (2%)	8 (9%)	0	1 (1%)
Other bacteria	12 (4%)	4 (5%)	0	2 (3%)
Fungi	3 (1%)	2 (2%)	0	0
Negative blood culture	16 (6%)	4 (5%)	4 (27%)	5 (7%)

(HACEK = *Haemophilus aphrophilus* – now known as *Aggregatibacter aphrophilus–Aggregatibacter actinomycetemcomitans; Cardiobacterium hominis; Eikenella corrodens;* and *Kingella kingae*)
Adapted from Moreillon P, Que YA. Infective endocarditis. Lancet 2004; 363:139–149.

- **Clinical features**

- Endocarditis can take either an acute or a more insidious ‘subacute’ form; the latter often passes undetected initially. There is considerable overlap because the clinical pattern is influenced not only by the organism but also by the site of infection, prior antibiotic therapy and the presence of a valve or shunt prosthesis. The subacute form may abruptly develop acute life-threatening complications, such as valve disruption or emboli.

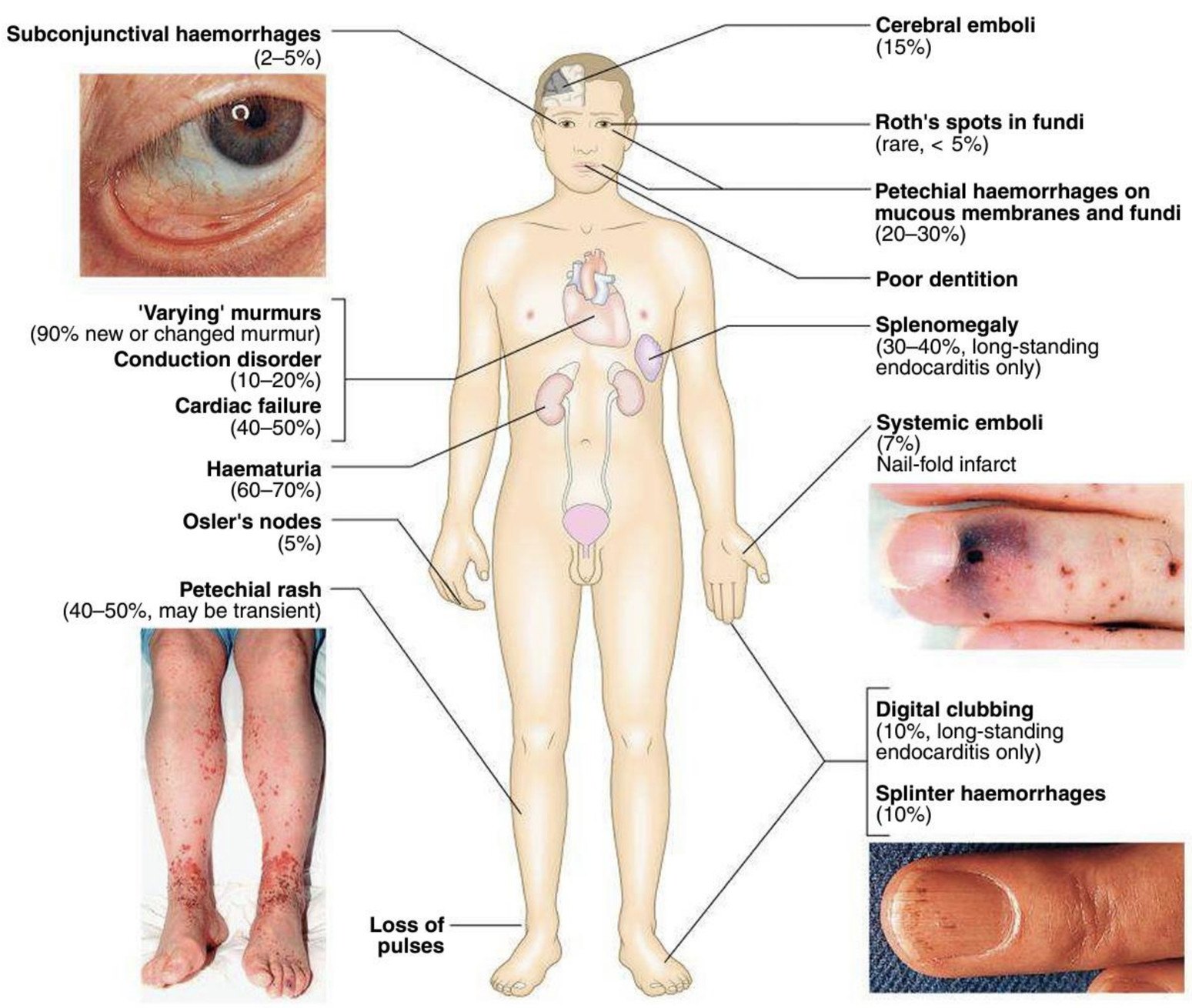

Fig. 16.87 **Clinical features that may be present in endocarditis.** *Insets (Petechial rash, nail-fold infarct) From Newby D, Grubb N. Cardiology: an illustrated colour text. Edinburgh: Churchill Livingstone, Elsevier Ltd; 2005.*

- **Subacute endocarditis**

- This should be suspected when a patient with congenital or valvular heart disease develops a persistent fever, complains of unusual tiredness, night sweats or weight loss, or develops new signs of valve dysfunction or heart failure. Less often, it presents as an embolic stroke or peripheral arterial embolism. Other features include purpura and petechial haemorrhages in the skin and mucous membranes, and 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 infections, the spleen and the liver may be considerably enlarged. Non-visible haematuria is common. The finding of any of these features in a patient with persistent fever or malaise is an indication for re-examination to detect hitherto unrecognised heart disease.

- **Acute endocarditis**

- This presents as a severe febrile illness with prominent and changing heart murmurs and petechiae. Clinical stigmata of chronic endocarditis are usually absent. Embolic events are common, and cardiac or renal failure may develop rapidly. Abscesses may be detected on echocardiography. Partially treated acute endocarditis behaves like subacute endocarditis.

- **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. Morbidity and mortality are high and revision surgery is often required. The range of organisms is similar to that seen in native valve disease, but when endocarditis occurs during the first few weeks after surgery it is usually due to infection with a coagulase-negative staphylococcus that was introduced during the perioperative period.

- **Investigations**

- Blood culture is the pivotal investigation to identify the organism that is the cause of 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. Isolation of a typical organism in more than one culture provides strong evidence in favour of the diagnosis . An in-dwelling line should not be used to take cultures. Both aerobic and anaerobic cultures are required.

- 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 visualised by TOE, which is particularly valuable for identifying abscess formation and investigating patients with prosthetic heart valves. Vegetations may be difficult to distinguish in the presence of an abnormal valve; 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.

- Elevation of the ESR, a normocytic normochromic anaemia, and leucocytosis are common but not invariable. Measurement of serum CRP is more reliable than the ESR in monitoring progress. Proteinuria may occur and non-visible haematuria is usually present. The ECG may show the development of AV block (due to aortic root abscess formation) and occasionally infarction due to emboli. The chest X-ray may show evidence of cardiac failure and cardiomegaly.

16.95 Diagnosis of infective endocarditis*

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

*Modified 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 endocarditis.

- **Management**

- A multidisciplinary approach, with cooperation between the physician, surgeon and microbiologist, increases the chance of a successful outcome. Any source of infection should be removed as soon as possible; for example, a tooth with an apical abscess should be extracted, or an in-dwelling catheter or device removed. 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 IV 6 times daily) should be considered (with or without gentamicin). If the presentation is acute, empirical therapy should be started with vancomycin (1 g IV twice daily) and gentamicin (1 mg/kg IV twice daily), with dose adjustment based on antibiotic levels. The same regimen is used in true penicillin allergy.

- 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 débridement of infected material and valve replacement may be required in a substantial proportion of patients, particularly those with Staph. aureus and fungal infections . Antimicrobial therapy must be started before surgery.

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	4 weeks	6 weeks
		1 mg/kg twice daily[2]	2 weeks	2 weeks
Penicillin MIC > 0.5 mg/L	Vancomycin IV and gentamicin IV	1 g twice daily[3]	4 weeks	6 weeks
		1 mg/kg twice daily[2]	4 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	4 weeks	6 weeks
		1 mg/kg twice daily[2]	4 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]	4 weeks	6 weeks
		1 mg/kg twice daily[2]	4 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	1 g twice daily[3]	4 weeks	–
	Rifampicin orally	300–600 mg twice daily	4 weeks	–
Staphylococci – prosthetic valve				
Meticillin-sensitive	Flucloxacillin IV	2 g 4–6 times daily	–	6 weeks
	and gentamicin IV	1 mg/kg twice daily[2]	–	6 weeks
	and rifampicin orally	300–600 mg twice daily	–	6 weeks
Meticillin-resistant, vancomycin MIC ≤ 2 mg/L, rifampicin-sensitive	Vancomycin IV	1 g twice daily[3]	–	6 weeks
	and rifampicin orally	300–600 mg twice daily	–	6 weeks

[1]When conditions in Box 16.97 are met, 2 weeks of benzylpenicillin and gentamicin (1 mg/kg twice daily) may be sufficient. Ceftriaxone 2 g once daily IV/IM can be used instead of benzylpenicillin for those with non-severe penicillin allergy. [2]Pre-dose gentamicin level should be ≤ 1 mg/L, post-dose 3–5 mg/L. Adjust dose according to levels and renal function. [3]Pre-dose vancomycin level should be 15–20 mg/L. Adjust dose according to levels and renal function. [4]Use 6 times daily if weight > 85 kg.
(IM = intramuscular; IV = intravenous; MIC = minimum inhibitory concentration)
Adapted from Gould FK, Denning DW, Elliott TS, et al. Guidelines for the diagnosis and antibiotic treatment of endocarditis in adults: a report of the working party of the British Society for Antimicrobial Chemotherapy. J Antimicrob Chemother 2012; 67:269–289.

16.97 Conditions for the short-course treatment of endocarditis caused by fully sensitive streptococci

- Native valve infection
- Minimum inhibitory concentration (MIC) $\leq$ 0.125 mg/L
- No adverse prognostic factors (heart failure, aortic regurgitation, conduction defect)
- No evidence of thromboembolic disease
- No vegetations $>$ 5 mm diameter

Clinical response within 7 days

16.98 Indications for cardiac surgery in infective endocarditis*

- 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

*Patients with prosthetic valve endocarditis or fungal endocarditis often require cardiac surgery.

- **Prevention**

- Antibiotic prophylaxis is no longer routinely given to people at risk of infective endocarditis undergoing interventional procedures. It can be considered in those at the highest risk of endocarditis.