Infective endocarditis

What is infective endocarditis?

Infective endocarditis (IE) is an infection of the endocardium of the heart. Infective endocarditis is a rare, life-threatening disease that has long-lasting effects even among patients who survive and are cured. It disproportionately affects those with underlying structural heart disease and is increasingly associated with patients who have intravascular prosthetic material. Once established, infective endocarditis can involve almost any organ system in the body [1] .

Infective endocarditis produces both intracardiac effects - eg, valvular insufficiency and a wide variety of systemic effects, both from emboli (sterile and infected) and a variety of immunological mechanisms.

It is a disease that is **easily overlooked** or misdiagnosed and clinicians should be vigilant and well versed in the manifestations of infective endocarditis to avoid missing the diagnosis.

Staphylococcus aureus spp., which has become the predominant causative organism in the developed world, leads to an aggressive form of the disease, often in the vulnerable or elderly [2] .

Who gets endocarditis? (Epidemiology) [3]

- IE occurs worldwide. In recent decades there has been a doubling of the average patient age and an increased prevalence in patients with indwelling cardiac devices [4] .
- The microbiology of the disease has also changed and staphylococci, most often associated with healthcare contact and invasive procedures, have overtaken streptococci as the most common cause [4] .

- Infective endocarditis has an annual incidence of up to 10 per 100,000 of the general population and carries a mortality of up to 30% at 30 days.
- Healthcare-related infections now account for 25-30% of newly reported cases of endocarditis.
- Figures for incidence are similar between countries. It is three times more common in men and increasing in elderly patients (25-50% of cases occur in the over-60s) often associated with other disease - eg, diabetes, cancer, alcoholism.

Risk factors for infective endocarditis

Cardiac conditions considered to increase a patient's risk of developing infective endocarditis[5] [6] :

- Valvular heart disease with stenosis or regurgitation.
- Valve replacement.
- Structural congenital heart disease, including surgically corrected or palliated structural conditions, but excluding:
    - Isolated atrial septal defect.
    - Fully repaired ventricular septal defect.
    - Fully repaired patent ductus arteriosus.
    - Closure devices that are judged to be endothelialised.
- Previous IE.
- Hypertrophic cardiomyopathy.

Other risk factors include recreational drug misuse and invasive vascular procedures.

Pathogenesis

All cases have a non-bacterial thrombotic endocarditis (a sterile fibrin-platelet vegetation) as the prerequisite for adhesion and invasion. The site of this thrombus is influenced by the Venturi effect, with deposition of thrombus on the low pressure side. There are differences in the different clinical situations.

Acute infective endocarditis
The thrombus may be produced either by the invading organism or by valvular trauma (pacing wires, catheters, etc).

Subacute infective endocarditis
Sufficient inoculum of bacteria required to allow invasion of the thrombus, bacteria clumping with production of agglutinating antibodies.

Non-bacterial thrombotic endocarditis
This can result from, for example, chronic kidney disease, neoplasia, systemic lupus erythematosus (SLE) or malnutrition.

The valves most commonly affected by IE are (in decreasing order of frequency):

- Mitral valve.
- Aortic valve.
- Combined mitral and aortic valve.
- Tricuspid valve.
- Pulmonary valve - rare.

The organisms responsible for infective endocarditis

- ***Staphylococcus aureus* spp.**:
  The most common cause of IE overall (acute and subacute); most common with prosthetic valves, acute IE and IE related to intravenous drug misuse. High mortality rate.
  Coagulase-negative *S. aureus*: causes subacute disease similar to *Streptococcus viridans*. Accounts for 30% of IE associated with prosthetic valves.
- **Streptococci**:
  - ***S. viridans***: 50-60% of subacute IE cases.
  - **Group D streptococci**: usually subacute and the third most common cause of IE.
  - ***Streptococcus intermedius***: acute and subacute infection. Causes 15% of all cases of IE.
  - **Group A, C and G streptococci**: acute IE is similar to that with *S. aureus*. High mortality (up to 70%).
  - **Group B streptococci**: acute disease, high mortality often requiring valve replacement. Occurs in pregnancy and the elderly particularly.
- ***Pseudomonas aeruginosa***: usually acute IE and requires surgery for cure.
- **HACEK organisms (*H*aemophilus** spp.,***A*ggregatibacter** *actinomycetemcomitans*, ***C*ardiobacterium** spp., ***E*ikenella** *corrodens*, ***K*ingella** *kingae*): usually subacute disease and about 5% of all IE.
- **Fungi**: cause subacute disease.
- **Enterococci**.

Infective endocarditis symptoms[5] [6]

See also the separate Cardiovascular History and Examination article.

- The clinical presentation is very variable. A high index of suspicion and low threshold for investigation to exclude infective endocarditis are therefore essential in higher risk groups.

- It may present as an acute, rapidly progressive infection but also as a subacute or chronic disease, with nonspecific symptoms - eg, fatigue, low-grade fever, flu-like illness, polymyalgia-like symptoms, loss of appetite, back pain, pleuritic pain, abdominal symptoms (may be pain, vomiting and appendicitis-like symptoms) and weight loss.
- The majority of patients present with fever, often associated with systemic symptoms of chills, poor appetite and weight loss.
- Heart murmurs are found in up to 85% and new murmurs have been recently reported in 48% of patients.
- Classic textbook signs may still be seen in the developing world but are increasingly uncommon in developed countries because patients present at an early stage of the disease.
- Immunological phenomena, such as splinter haemorrhages, Roth's spots and glomerulonephritis, are now less common but emboli to brain (cerebrovascular accident), lung or spleen occur in 30% of patients and are often the presenting feature.
- May present with congestive cardiac failure
- Atypical presentation (eg, no fever) is more common in the elderly, after antibiotic pre-treatment, in the immunocompromised patient and in IE involving less virulent or atypical organisms.
- The diagnosis of IE should also be considered in patients who present with a stroke or transient ischaemic attack and a fever.

Examination

- **Fever**: elderly, chronically ill patients with subacute IE may not have fever but the majority do.
- **Heart murmurs**:
    - Most patients have a murmur.
    - The exception is right-sided IE where one third have murmurs.
    - Only 15% have the classic 'changing murmur'.
    - The most common murmur is aortic regurgitation.

- **Petechiae**:
    - Conjunctivae.
    - Hands and feet (dorsum).
    - Chest and abdominal wall.
    - Oral mucosae and soft palate.
- **Splinter or subungual haemorrhages**: linear and red.
- **Osler's nodes**: small tender red-to-purple nodules on the pulp of the terminal phalanges of the fingers and toes
- **Clubbing**: only 10% of cases and usually in long-standing subacute IE.
- **Roth's spots**: retinal haemorrhages with pale centres.
- **Janeway's lesions**: irregular painless erythematous macules on the thenar and hypothenar eminence (usually with acute IE and *S. aureus*).
- **Arthritis**:
    - With subacute IE, usually asymmetric and up to three joints affected (fluid sterile).
    - Acute IE can give acute septic monoarticular arthritis.
- **Splenomegaly**: most often observed in long-standing subacute disease and often persisting after treatment.
- **Meningism/meningitis**: purulent disease occurs in acute IE and aseptic variety in subacute IE.

Criteria for consideration and investigation of possible infective endocarditis [5]

- A febrile illness and a murmur of new valvular regurgitation.
- A febrile illness, a pre-existing at-risk cardiac lesion (see 'Risk factors', above) and no clinically obvious site of infection.

- A febrile illness associated with any of:
    - Predisposition and recent intervention with associated bacteraemia.
    - Evidence of congestive heart failure.
    - New conduction disturbance.
    - Vascular or immunological phenomena: embolic event, Roth's spots, splinter haemorrhages, Janeway's lesions, Osler's nodes.
    - A new stroke.
    - Peripheral abscesses (renal, splenic, cerebral, vertebral) of unknown cause.
- A protracted history of sweats, weight loss, anorexia or malaise and an at-risk cardiac lesion (see 'Risk factors', above).
- Any new unexplained embolic event (eg, cerebral or limb ischaemia).
- Unexplained, persistently positive blood cultures.
- Intravascular catheter-related bloodstream infection with persistently positive blood cultures 72 hours after catheter removal.

Differential diagnosis

Patients present to a variety of specialists who may consider a range of alternative diagnoses, including chronic infection, rheumatological and autoimmune disease or malignancy. Some of the more unusual diseases which may also have similar complex and varied manifestations include:

- SLE.
- Cardiac tumours - eg, atrial myxoma.
- Lyme disease.
- Antiphospholipid syndrome.
- Polymyalgia rheumatica.
- Reactive arthritis.

Presentations that may cause difficulty with diagnosis include:

- Acute meningitis - signs and symptoms but with sterile CSF.
- Hemiplegia from emboli in the middle cerebral artery (50% of patients may be first manifestation; has high mortality).
- Renal infarcts causing painless haematuria.
- Splenic infarction causing pain.
- Sight loss from retinal artery occlusion.
- Myocardial infarction from emboli in the coronary artery.
- Pulmonary emboli.
- Interstitial nephritis or proliferative glomerulonephritis from deposition of circulating immune complexes.
- Acute kidney injury or chronic kidney disease which may result.
- Musculoskeletal symptoms (nearly half of patients) - often from immunologically mediated synovitis.
- Immune-mediated vasculitis (causing Osler's nodes and Roth's spots).
- Palpitations from immune-mediated myocarditis.
- Back pain (15% of patients) may have origin in immune complex deposition in disc spaces.

Investigations[5]

Although echocardiography is still the mainstay imaging test, it misses up to 30% of cases. Newer imaging tests, such as 4-dimensional CT, fluorodeoxy-glucose PET, and leukocyte scintigraphy, are increasingly used as alternative or adjunct tests for select patients. They improve the sensitivity of diagnosis, especially in the setting of a prosthetic valve[7] .

- Nonspecific signs of infection - eg, elevated CRP or ESR, leukocytosis, anaemia and microscopic haematuria.
- CXR: as part of the initial assessment.

- ECG is useful to detect the 10% of patients who will develop conduction defects.
- Blood cultures:
    - Should be taken prior to starting treatment in all cases. Meticulous aseptic technique is required.
    - In patients with a chronic or subacute presentation, three sets of blood cultures should be taken from peripheral sites with at least six hours between them prior to commencing antimicrobial therapy.
    - In patients with suspected IE and severe sepsis or septic shock at the time of presentation, two sets of blood cultures should be taken at different times within one hour prior to commencement of empirical therapy.
    - Bacteraemia is continuous in IE rather than intermittent, so positive results from only one set out of several blood cultures should be regarded with caution.
    - If a stable patient has suspected IE but is already on antibiotic treatment, consideration should be given to stopping treatment and performing three sets of blood cultures off antibiotics.
    - Antibiotic therapy may need to be stopped for 7-10 days before blood cultures become positive.
    - Routine incubation of blood cultures for more than seven days is not necessary. Once a microbiological diagnosis has been made, routine repeat blood cultures are not recommended. Blood cultures should be repeated if a patient is still febrile after seven days of treatment.
    - When the causative micro-organism has been isolated, the minimum inhibitory concentration (MIC) of the chosen antimicrobial should be established.
    - Blood cultures are negative in 2-40% of cases of endocarditis, with some studies reporting blood culture-negative rates up to 71% [8] .

- Echocardiography:
    - Echocardiography must be performed as soon as possible (ideally within 24 hours) in all patients with suspected IE.
    - Transthoracic echocardiography (TTE) is the initial investigation of choice. In cases with an initially negative TTE/transoesophageal echocardiography (TOE) examination, repeat TTE/TOE should be performed 7-10 days later if the clinical suspicion of IE remains high.
    - All patients with *S. aureus* bacteraemia or candidaemia require echocardiography (ideally within the first week of treatment or within 24 hours if there is other evidence to suggest IE).
    - TTE is recommended at completion of antibiotic therapy for evaluation of cardiac and valve morphology and function. Follow-up echocardiography should be performed if there is evidence of cardiac complications or a suboptimal response to treatment.
- Other imaging modalities used include MRI, nuclear imaging and multislice CT coronary angiography [6] .
- Serology:
    - In patients with blood culture-negative infective endocarditis, serological testing for *Coxiella* and *Bartonella* species should be performed.
    - Consider brucellosis in patients with negative blood cultures and a risk of exposure (dietary, occupational or travel).
    - Candida antibody and antigen tests should not be used to diagnose candidal IE because there is currently no evidence to support their use and therefore relying on these tests may lead to inappropriate treatment.

- Investigation of excised heart valves:
    - Samples of valve or other infected tissue removed at the time of surgery should be sent for microbiological and histopathological investigation.
    - Samples of excised heart valve (or tissue from embolectomy) from cases of culture-negative IE should be referred for broad-range bacterial PCR and sequencing.

Diagnostic criteria [5]

Modified Duke criteria for diagnosis of infective endocarditis: clinical criteria for definite IE requires two major criteria, one major and three minor criteria, or five minor criteria.

Major criteria

- Positive blood culture for infective endocarditis: typical micro-organism consistent with IE from two separate blood cultures.
- Evidence of endocardial involvement:
    - Positive echocardiogram for infective endocarditis:
        - Oscillating intracardiac mass on valve or supporting structures, in the path of regurgitant jets, or on implanted material in the absence of an alternative anatomical explanation; or
        - Abscess; or
        - New partial dehiscence of prosthetic valve); or
        - New valvular regurgitation (worsening or changing of pre-existing murmur not sufficient).

Minor criteria

- Predisposition: predisposing heart condition or intravenous drug use.
- Fever: temperature >38°C.

- Vascular phenomena: major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, conjunctival haemorrhages and Janeway's lesions.
- Immunological phenomena: glomerulonephritis, Osler's nodes, Roth's spots and rheumatoid factor.
- Microbiological phenomena: positive blood culture but does not meet a major criterion as noted above or serological evidence of active infection with organism consistent with infective endocarditis.
- PCR: broad-range PCR of 16S (polymerase chain reaction using broad-range primers targeting the bacterial DNA that codes for the 16S ribosomal subunit).
- Echocardiographic findings consistent with IE but do not meet a major criterion as noted above.

Blood culture-negative IE (BCNIE) refers to infective endocarditis in which no causative micro-organism can be grown using the usual blood culture methods. BCNIE can occur in up to 31% of all cases of IE and most commonly arises as a consequence of previous antibiotic administration[6] .

Infective endocarditis treatment and management[5] [6] [9]

Have a high index of suspicion. Admit any patient with suspected IE to hospital for full investigation. A cardiologist and infection specialist should be closely involved in the diagnosis, treatment and follow-up of patients with IE.

Antimicrobial therapy

Antibiotic management of endocarditis, especially in culture-negative cases, is complex. The choice of regimens and ongoing input should be provided by an infection specialist[3] .

Oral therapy for endocarditis has been used but is rarely advocated in guidelines because of concerns about efficacy. In general, intravenous therapy is recommended to ensure adequate dosing and administration. Occasionally, especially in intravenous drug users, problems obtaining or maintaining safe intravenous access mean that oral therapy may be the safest treatment option. Agents with oral bioavailability that is close to that achieved with intravenous administration can be given. Ciprofloxacin, linezolid and rifampicin have excellent oral bioavailability.

Home/community/outpatient intravenous therapy is an appropriate method for managing selected patients with IE - eg, those who are stable and responding well to therapy without signs of heart failure, have no indications for surgery (see below) and no uncontrolled extracardiac foci of infection. *S. aureus* is associated with highest mortality and complications, and caution is therefore advised where this is the cause. Ceftriaxone, teicoplanin, daptomycin and vancomycin are suitable agents for home/community/outpatient therapy for endocarditis.

Initial empirical therapy while awaiting culture results

- Native valve endocarditis (NVE) - indolent presentation: amoxicillin AND (optional) gentamicin. The role of gentamicin is controversial before culture results are available.
- NVE, severe sepsis (no risk factors for *Enterobacteriaceae*, *Pseudomonas* spp.): vancomycin (if allergic to vancomycin, replace with daptomycin) AND gentamicin. If there are concerns about nephrotoxicity/acute kidney injury, use ciprofloxacin in place of gentamicin.
- NVE, severe sepsis AND risk factors for multiresistant *Enterobacteriaceae*, *Pseudomonas* spp: vancomycin AND meropenem.
- Prosthetic valve endocarditis (PVE): pending blood cultures or with negative blood cultures: vancomycin AND gentamicin AND rifampicin.

Staphylococcal endocarditis

Intravenous therapy for four weeks is recommended for staphylococcal NVE, which should be extended to at least six weeks in patients with intracardiac prostheses, secondary lung abscesses and osteomyelitis. Routine switch to oral antimicrobials is not recommended.

- NVE, meticillin-susceptible staphylococci: flucloxacillin.
- NVE, meticillin-resistant: vancomycin AND rifampicin.
- NVE, meticillin-resistant, vancomycin-resistant: daptomycin AND rifampicin OR gentamicin.
- PVE, meticillin, rifampicin-susceptible staphylococci: flucloxacillin AND rifampicin AND gentamicin.
- PVE, meticillin-resistant, vancomycin-susceptible or penicillin allergy: vancomycin AND rifampicin AND gentamicin.
- PVE, meticillin-resistant, vancomycin-resistant: daptomycin AND rifampicin AND gentamicin.

Streptococcal endocarditis

- Benzylpenicillin monotherapy; ceftriaxone monotherapy; benzylpenicillin AND gentamicin; ceftriaxone AND gentamicin.
- Treatment of streptococci in patients with significant penicillin allergy: vancomycin AND gentamicin; teicoplanin AND gentamicin.

Enterococcal endocarditis

- Amoxicillin OR penicillin AND gentamicin; vancomycin AND gentamicin; teicoplanin AND gentamicin; amoxicillin (for amoxicillin-susceptible AND high-level gentamicin resistant isolates).

HACEK endocarditis

- Treatment should be with a b-lactamase-stable cephalosporin or amoxicillin if the isolate is susceptible.
- Gentamicin should only be added for the first two weeks of therapy.
- Ciprofloxacin can be considered as an alternative agent.

- NVE should receive four weeks and PVE six weeks of treatment.

Q fever

- Doxycycline and hydroxychloroquine (both antibiotics for at least 18 months and up to four years).
- Doxycycline and ciprofloxacin (for at least three years)

Bartonella

- Amoxicillin AND gentamicin (if penicillin-allergic then use tetracycline).
- Doxycycline AND gentamicin.

Fungal endocarditis
Antifungal agents used include fluconazole, voriconazole, amphotericin, micafungin, caspofungin, anidulafungin, posaconazole and flucytosine. Itraconazole should not be used.

Candidal endocarditis
Initial treatment should be with an echinocandin or amphotericin. Surgical valve replacement is recommended.

Aspergillus endocarditis
Initial treatment should be with voriconazole. Surgical valve replacement is mandatory for survival.

Surgery

A surgical opinion should be sought at the earliest opportunity for every patient with endocarditis affecting intracardiac prosthetic material.

Antibiotics are the standard treatment for native valve infective endocarditis, with surgery primarily reserved for patients with heart failure or inadequate response to antibiotic treatment.

The timing and indications for surgical intervention to prevent systemic embolism in IE remain controversial. A trial to compare clinical outcomes of early surgery and conventional treatment in patients with left-sided IE, severe valve disease and large vegetations found that early surgery in patients with IE and large vegetations significantly reduced mortality from embolic events by effectively decreasing the risk of systemic embolism [10] .

A surgical opinion should be sought for any of the following indications [5] :

Heart failure

Aortic or mitral infective endocarditis with:

- Severe acute regurgitation or valve obstruction causing refractory pulmonary oedema/shock (emergency).
- Fistula into a cardiac chamber or pericardium causing refractory pulmonary oedema/shock (emergency).
- Severe acute regurgitation or valve obstruction and persisting heart failure or echocardiographic signs of poor haemodynamic tolerance (urgent).
- Severe regurgitation and no heart failure (elective).

Uncontrolled infection

- Locally uncontrolled infection including abscess, false aneurysm, enlarging vegetation (urgent).
- Persisting fever and positive blood culture for at least ten days after commencing appropriate antimicrobial therapy (urgent).
- Infection caused by fungi or multiresistant micro-organisms (urgent/elective).

Prevention of embolism

- Aortic or mitral IE with large vegetations (>10 mm) resulting in one or more embolic episodes despite appropriate antibiotic therapy (urgent).
- Aortic or mitral IE with large vegetations (>10 mm) and other predictors of complicated course like heart failure, persistent infection or abscess (urgent).

- Isolated very large vegetations >15 mm (urgent).

Infective endocarditis complications

These are an inherent part of the progression of the disease. Potential complications of IE include[6] :

- Myocardial infarction, pericarditis, cardiac arrhythmias.
- Heart valve insufficiency.
- Congestive heart failure.
- Sinus of Valsalva aneurysm.
- Aortic root or myocardial abscesses.
- Arterial emboli, infarctions, mycotic aneurysms.
- Arthritis, myositis.
- Glomerulonephritis, acute kidney injury.
- Stroke syndromes.
- Mesenteric or splenic abscess or infarction.

Infective endocarditis prognosis

Although novel diagnostic and therapeutic strategies have emerged, the overall one-year mortality has not improved and remains at 30%[4] . However, the prognosis varies markedly according to a variety of factors. Predictors of poor outcome include[6] :

- Patient characteristics: older age, prosthetic valve IE, diabetes, comorbidity (eg, frailty, immunosuppression, renal or pulmonary disease).
- Clinical complications of IE: heart failure, renal failure, greater than moderate area of ischaemic stroke, brain haemorrhage, septic shock.
- Micro-organism: *S. aureus*, fungi, non-HACEK Gram-negative bacilli.

- Echocardiogram findings: peri-annular complications, severe left-sided valve regurgitation, low left ventricular ejection fraction, pulmonary hypertension, large vegetations, severe prosthetic valve dysfunction, premature mitral valve closure and other signs of elevated diastolic pressures.

Cure rates

- NVE:
    - *S. viridans* 98% cure rate.
    - *S. aureus* 60-70% cure rate with worse results in those NOT abusing intravenous drugs.
    - Fungal infections - cure rate less than 50%.
- PVE:
    - Cure rates at least 10% lower than above for each variety.
    - Surgery needed more often.

Mortality

- Mortality rates in NVE range from 16-27%. Mortality rates in patients with PVE are higher.
- Increased mortality rates are associated with increased age, infection involving the aortic valve, development of congestive heart failure, central nervous system complications and underlying disease - eg, diabetes.
- Mortality rates also vary with the infecting organism:
    - Acute endocarditis due to *S. aureus* is associated with a high mortality rate (30-40%), except when it is associated with intravenous drug use.
    - Endocarditis due to streptococci has a mortality rate of approximately 10%.

Prevention

The use of antibiotic prophylaxis for prevention of infective endocarditis is controversial. In recent years, guidelines have advised a much more restricted use of antibiotic prophylaxis [11] .

See the separate Prevention of Infective Endocarditis article.

Further reading

- Prophylaxis against infective endocarditis: Antimicrobial prophylaxis against infective endocarditis in adults and children undergoing interventional procedures; NICE Clinical Guideline (March 2008 - last updated July 2016)
- Guidelines on the management of valvular heart disease; European Society of Cardiology (2012)
- Pettersson GB, Coselli JS, Pettersson GB, et al; 2016 The American Association for Thoracic Surgery (AATS) consensus guidelines: Surgical treatment of infective endocarditis: Executive summary. J Thorac Cardiovasc Surg. 2017 Jun;153(6):1241-1258.e29. doi: 10.1016/j.jtcvs.2016.09.093. Epub 2017 Jan 24.

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