

# INFECTIVE ENDOCARDITIS

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Infective endocarditis (IE) is defined as infection of the endocardial surfaces of the heart. In the majority of cases, one or more heart valves is involved. However, arteriovenous and arterioarterial shunts, septal defects and coarctation abnormalities of the aorta can also be affected. Some of the more common congenital heart lesions at risk for IE and other medical risk factors are as follows:

## Risk factors for IE

1. Mitral valve prolapse with regurgitation.
2. Aortic valve/mitral valve degenerative disease.
3. Congenital heart disease.
4. Rheumatic fever.
5. Hypertrophic cardiomyopathy.
6. Increasing age.
7. Males>females.
8. Diabetes mellitus.
9. Immunosuppression/immunocompromise.

## Congenital heart disease and endocarditis

1. Patent ductus arteriosus.
2. Ventricular septal defect.
3. Bicuspid aortic valve.
4. Coarctation of the aorta.
5. Pulmonary stenosis.
6. Hypertrophic cardiomyopathy.
7. Marfan's syndrome (aortic incompetence).

The term 'IE' replaced bacterial endocarditis in the middle of the twentieth century when it became apparent that practically any infectious agent can infect the valves and endocardial surface of the heart. From a classification point of view, IE can be studied in three groups:

- native valve endocarditis (NVE);
- prosthetic valve endocarditis (PVE); and
- endocarditis related to intravenous drug use (IDU).

This article will deal predominantly with NVE and IDU endocarditis. Previously, IE was also further subdivided into 'acute' and 'sub-acute'. This subdivision today is really only of historical interest as it was based on the usual progression pattern of untreated disease. With the development of antimicrobial therapy, severe forms of untreated acute disease became less prevalent. Despite antibiotics, however, IE today is on the increase. The reasons for this are listed below.

## Increasing incidence

1. Older population with degenerative valve disease.
2. More prosthetic valves.
3. More adults surviving with congenital heart disease.
4. Improved diagnosis.
5. Improved survival with chronicity and recurrence.
6. IDU more prevalent.

Probably the most important contributing factor to the incidence of IE in recent times is IDU. This has led to more right heart endocarditis, more staphylococcal disease and more unusual pathogens – as a result of HIV certainly but also as a result of poor hygiene and shared dirty needles. The features of IDU are outlined below.

## IDU endocarditis – features and complications

### Endocarditis and IDU

- More frequent bacteraemias, especially with skin organisms and oral flora.
- Increased exposure to enterococci and Gram-negative bacilli (GNB) from the gastrointestinal tract (GIT).
- Association with acquired immune deficiency leads to increased susceptibility to opportunistic infections.
- Right heart more commonly affected due to intravenous injection.
- Different valve representation: tricuspid>mitral>aortic>pulmonary.
- Increased septic emboli to lungs and consequent pneumonia due to right heart involvement.

### Complications in IDU endocarditis

- Congestive cardiac failure (CCF) due to valvular insufficiency.
- Chronic renal failure (CRF).
- CNS haemorrhage and emboli.
- Ruptured mycotic aneurysm.
- Pulmonary embolism (PE).

### Clinical manifestations

Although IE predominantly affects the heart, any organ in the body can become secondarily involved in the disease. The clinical presentation is therefore highly variable, making diagnosis very difficult.

Non-specific symptoms – anorexia, weight loss, nausea, vomiting, malaise, fatigue, chills and night sweats – are common.

Fever is present in up to 95% of cases although it is rarely greater than 40°C. It is typically remittent in nature and responds well to antibiotics. If the fever is prolonged (over two weeks' duration) despite antibiotics, it suggests a specific infectious agent, i.e. *Staphylococcus aureus*, GNB, fungi or culture-negative endocarditis. Prolonged fever also carries a worse prognosis as the fever itself typically reflects ongoing embolisation, intracardiac abscess formation or tissue infarction. If none of these phenomena is found in a patient with prolonged fever, the possibility of pulmonary embolism or a drug fever needs to be considered.

Murmurs are heard in over 85% of patients, although the classic findings of the changing murmur and new regurgitant murmur are found in less than 10%. Those who do develop a new regurgitant murmur typically develop CCF. It should be noted that CCF is the leading cause of mortality in IE and its incidence is, like that of the disease itself, also increasing. Unlike CCF, the prevalence of the classic peripheral stigmata of endocarditis is decreasing. This is presumably related to the earlier diagnosis of cases of IE and improved antibiotic treatment once diagnosis is confirmed.

Clubbing occurs in 10-20% and splinter haemorrhages, although not specific for IE, are commonly found on examination. Petechiae are present in 20-40% and usually affect conjunctivae, oral mucous membranes and extremities. These are felt to be either a vasculitic or an embolic phenomenon. Osler nodes (fingers), Janeway lesions (palms) and Roth spots (retina) are rare overall, although they may be seen in up to one quarter of cases of chronic endocarditis. Right-sided endocarditis is not typically associated with peripheral stigmata.

The spleen can be frequently involved in IE as a result of septic embolisation. These septic emboli can go on to form abscesses. However, although splenomegaly is a traditional association with IE, it too seems to be decreasing in incidence as diagnostic modalities and antimicrobial therapies improve.

It should be remembered that any organ — not only the spleen — can be affected by a major embolic event in IE. These occur in over 33% of cases and represent the second most common complication after CCF. Splenic, renal, retinal, pulmonary, coronary and cerebral arteries may all be embolised, as indeed may large peripheral vessels, i.e. femoral, brachial and popliteal.

Neurological symptomatology is also caused by mycotic aneurysm formation of the cerebral vasculature. These usually result in catastrophic subarachnoid haemorrhages, but may present with practically any central nervous system signs. Neurological deterioration in any patient with IE is a poor prognostic sign.

Renal failure in IE is due to an immune complex-mediated glomerulonephritis and is associated with low serum complement levels. The incidence of uraemia is also on the decrease since the dawn of the antibiotic era and most cases of renal failure are found to be reversible with the introduction of appropriate antibiotics.

Symptoms	Signs
Fever	Fever
Chills	Murmur (new/changing)
Weakness	Embolic phenomena
Dyspnoea	Skin lesions: Osler nodes
Sweats	Janeway lesions
Anorexia	Petechiae
Weight loss	Splinter haemorrhages
Malaise	Splenomegaly
Cough	Septic complications
Skin lesions	(pneumonia, meningitis)
Stroke	Mycotic aneurysms
Nausea/vomiting	Clubbing
Headache	Retinal lesions (Roth spots)
Myalgia/arthralgia	Renal failure
Oedema	
Chest pain	
Abdominal pain	
Delirium/coma	
Haemoptysis	
Back pain	

Table 1. Clinical manifestations of IE

## Diagnosis

Diagnostic criteria (Beth Israel – von Reyn et al) for IE were first published in 1982. The format of these criteria followed along the same lines as the Duckett-Jones criteria for the diagnosis of acute rheumatic fever. The Beth Israel criteria did not, however, use echo findings nor was the isolation of a 'typical' organism considered.

Over the past 20 years since the criteria were published, echocardiography has moved to the forefront of diagnostic techniques for IE. Also during that time, microbiological techniques for culture and identification of infectious agents causing IE have advanced. As a result of this, in 1994, a team from Duke University proposed a new set of diagnostic criteria for IE.

The Duke criteria have been compared to the Beth Israel criteria in 11 major studies since their introduction. All of these demonstrated increased sensitivity of the new criteria in the diagnosis of IE. The main differences in the Duke criteria are as follows:

- echo findings introduced as a major criterion;
- isolation of 'typical' organism for IE introduced as a major criterion; and
- addition of recent IDU as a minor criterion.

## Diagnostic criteria

Using the diagnostic criteria set out below — Duke Criteria — the diagnosis of endocarditis can be definite, possible or rejected.

### Definite

- requires two major criteria or
- requires one major + three minor or
- requires five minor.

Presentations: A clear, colourless to pale yellow solution available in prefilled syringes containing: Clexane Syringes (100mg/ml): 20mg enoxaparin sodium (equivalent to 2,000 IU anti-Xa activity) in 0.2ml water for injections, 40mg enoxaparin sodium (equivalent to 4,000 IU anti-Xa activity) in 0.4 ml water for injections, 60mg enoxaparin sodium (equivalent to 6,000 IU anti-Xa activity) in 0.6ml water for injections, 80mg enoxaparin sodium (equivalent to 8,000 IU anti-Xa activity) in 0.8ml water for injections, 100mg enoxaparin sodium (equivalent to 10,000 IU anti-Xa activity) in 1.0ml water for injections. Clexane Forte Syringes (150mg/ml): 120mg enoxaparin sodium (equivalent to 12,000 IU anti-Xa activity) in 0.8ml water for injections., 150mg enoxaparin sodium (equivalent to 15,000 IU anti-Xa activity) in 1.0ml water for injections. Indications: ■ The prophylaxis of thromboembolic disorders of venous origin, in particular those which may be associated with orthopaedic or general surgery. Longer treatment duration may be appropriate in some patients following hip replacement, enoxaparin sodium may be continued for as long as there is a risk of venous thromboembolism and until the patient is ambulatory. ■ The prophylaxis of venous thromboembolism in medical patients bedridden due to acute illnesses including cardiac insufficiency, respiratory failure or severe infections. ■ The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both. ■ Treatment of unstable angina and non-Q-wave myocardial infarction, administered concurrently with aspirin. ■ The prevention of thrombus formation in the extracorporeal circulation during haemodialysis. Dosage and Administration: Adult: Prophylaxis of venous thromboembolism. ■ In patients with a low to moderate risk of thromboembolism, such as in general surgery, the recommended dose of Clexane is 20mg (2,000 IU) once daily by subcutaneous injection. Treatment should be continued for 7 to 10 days or until the risk of thromboembolism has diminished. In patients undergoing surgery, the initial dose should be given approx. 2 hours pre-operatively. In patients with a higher risk of venous thromboembolism, such as in orthopaedic surgery, the dose should be increased to 40mg (4,000 IU) administered once daily by subcutaneous injection with the initial dose being given approx. 12 hours pre-operatively. Continued therapy with 40mg once daily for three weeks following initial therapy has been proven to be beneficial in patients post hip replacement. ■ In medical patients the recommended dose of Clexane is 40mg (4,000 IU) once daily by subcutaneous injection. Treatment is prescribed for a minimum of 6 days and continued until the full return of ambulation, for a maximum of 14 days. Where a patient is clinically adjudged to be at continued significant risk for thromboembolic events beyond 14 days a decision to prolong prophylaxis should be made on an individual basis. ■ The treatment of venous thromboembolic disease presenting with deep vein thrombosis, pulmonary embolism or both. Clexane can be administered subcutaneously either as a single injection of 1.5mg/kg (150 IU/kg) or a twice daily injections of 1mg/kg (100 IU/kg) every 12 hours. In patients with a complicated thromboembolic disorder, a dose of 1mg/kg (100 IU/kg) administered twice daily is recommended. Treatment is usually prescribed for at least 5 days and until adequate oral anticoagulation is established. ■ Treatment of unstable angina and non-Q-wave myocardial infarction: The recommended dose is 1mg/kg (100IU/kg) every 12 hours by subcutaneous injection, administered concurrently with oral aspirin (100 to 325mg once daily). Treatment with enoxaparin sodium in these patients should be prescribed for a minimum of 2 days and continued until clinical stabilisation. The usual duration of treatment is 2 to 8 days. ■ Prevention of extracorporeal thrombus formation during haemodialysis: A dose equivalent to 1mg/kg (100 IU/kg) introduced into the arterial line of circuit at the beginning of the dialysis session is usually sufficient for a 4 hour session. If fibrin rings are found, such as after a longer than normal session, a further dose of 0.5 to 1mg/kg (50 to 100 IU/kg) may be given. For patients with a high risk of haemorrhage the dose should be reduced to 0.5mg/kg (50 IU/kg) for double vascular access or 0.75mg/kg (75 IU/kg) for single vascular access. Elderly: No dose adjustment is necessary. Children: Dosage not established. Contra-indications: In patients with acute bacterial endocarditis, major bleeding disorders, thrombocytopenia in patients with a positive "in vitro" aggregation test in the presence of enoxaparin, active gastric or duodenal ulcer, hiatal ulceration, hypersensitivity to enoxaparin, stroke (unless due to systemic emboli), jaundice, threatened abortion, retinopathy or in other patients with increased risk of haemorrhage. Warning/Precautions: Clexane must not be administered by the intramuscular route. Clexane should be used with caution in patients with a history of heparin-induced thrombocytopenia, severe hepatic or renal insufficiency, severe arterial hypertension, history of gastrointestinal ulceration, recent ischaemic stroke, diabetic retinopathy, recent cerebral surgery or trauma. Care should be taken for the concurrent use of Clexane and spinal/epidural anaesthesia in relation to neuraxial haematoma. The use of Clexane cannot be recommended in patients with prosthetic heart valves. Careful monitoring is advised in the elderly and in low weight patients (women < 45kg, men < 57kg). As different low molecular weight heparins may not be equivalent, alternative products should not be introduced during a course of treatment. Pregnancy: As a precaution Clexane should not be used during pregnancy. Lactation: Lactating mothers receiving Clexane should be advised to avoid breast-feeding. Interaction: Use with care in patients receiving systemic salicylates, aspirin and NSAID's. Adverse Reactions: Pain, haematoma and mild local irritation may occur following injection. Bleeding may occur during enoxaparin therapy in the presence of associated risk factors. Exceptional cases of skin necrosis at the injection site have been reported with heparins and low molecular weight heparins. These phenomena are usually preceded by purpura or erythematous plaques, infiltrated and painful. Although rare, cutaneous or systemic allergic reactions may occur. Thrombocytopenia may occur rarely and asymptomatic and reversible increases in platelet counts and liver enzyme levels have been reported. Pharmaceutical Precautions: Do not mix Clexane with other injections or infusions. Do not store above 25°C. Do not refrigerate or freeze. Legal Category: S1A. Product Authorisation Number: PA 540/97/1-2. Clexane is a registered Trademark. Aventis, 18 Riverwalk, National Digital Park, Citywest Business Campus, Dublin 24. Telephone (01) 4035600. Updated: May 2003 Ref 1 - SPC, Ref 2 - Data on file.

**Possible**

Findings consistent with IE that fall short of 'definite', but not 'rejected'.

**Rejected**

- Firm alternate diagnosis explaining evidence of endocarditis or
- resolution of endocarditis syndrome, with antibiotic therapy for four days or less or
- no pathological evidence of endocarditis at surgery or autopsy, after antibiotic therapy for four days or less.

**Major criteria**

1. Positive blood cultures for IE
  - Typical organism from two separate blood cultures
  - *Viridans streptococci*, *Streptococcus bovis*, HACEK (*Haemophilus*, *Actinobacillus*, *Cardiobacterium*, *Eikenella* and *Kingella*) organism community-acquired *S. aureus* or enterococci in the absence of a primary focus, or
  - persistently positive blood cultures for any micro-organism (i.e. from blood cultures drawn more than 12 hours apart), or
  - all of three, or majority of four or more separate blood cultures, with first and last specimens drawn at least one hour apart.

2. Evidence of endocardial involvement on echo
  - Findings on echocardiogram positive for IE
  - Oscillating intracardiac mass on valve or supporting structures or in the path of regurgitant jets, or on iatrogenic devices, in the absence of an alternative anatomic explanation, or
  - abscess, or
  - new partial dehiscence of prosthetic valve, or
  - new valvular regurgitation (increase or change in pre-existing murmur not sufficient).

**Minor criteria**

1. Predisposition: predisposing heart condition or IDU.
2. Fever >38°C (100.4°F).
3. Vascular phenomena: arterial embolism, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage, Janeway lesions.
4. Immunological phenomena: glomerulonephritis, Osler nodes, Roth spots, rheumatoid factor.

5. Echocardiogram: findings consistent with IE but not meeting major criterion above.

6. Microbiological evidence: positive blood culture but not meeting major criterion above or serological evidence of active infection with organism consistent with IE.

**Laboratory manifestations of IE**

- Bacteraemia (continuous)
- Anaemia (MCV normal)
- Leukocytosis
- Proteinuria
- Haematuria (microscopic)
- Elevated serum creatinine
- Raised ESR and CRP
- Rheumatoid factor positivity (about 50%)
- Circulating immune complexes (disappear on cure)
- Decreased serum complement level.

The major pathogens that cause IE are listed in Table 2. Between them, streptococci and staphylococci are probably responsible for over 90% of cases. Despite the fact that they are both Gram-positive cocci, they can cause very different forms of the disease.

Agent	% of cases
<b>Streptococci</b>	60-80
Viridans	30-40
Enterococci	5-18
Other	5-25
<b>Staphylococci</b>	20-35
Coagulase-positive	10-27
Coagulase-negative	1-3
<b>Gram-negative aerobic bacilli</b>	1.5-13
<b>Fungi</b>	2-4
<b>Miscellaneous bacteria</b>	<5
<b>Mixed infections</b>	1-2
<b>Culture-negative</b>	<5-24

Table 2. Causative organisms

**Streptococci**

Streptococci are Gram-positive, catalase-negative organisms that can grow in both aerobic and anaerobic (facultatively) conditions. As a group, they are responsible for more than half of all cases of endocarditis. Not all streptococci, however, cause the same severity of disease nor do they carry the same prognosis.

Streptococci are classified based on their haemolysis pattern on blood agar. The two most important clinical groupings are the viridans and the beta-haemolytic.