Infective Endocarditis

Introduction

Infective endocardium is a condition characterized by the patient's endocardium is colonized by the microbiological agents, that microbes are actively multiplying within the endocardium & damaging it. The heart's inner lining (the **endocardium**) becomes **inflamed** secondary to an **infection**.

Prevalence

Infective endocarditis occurs worldwide and has, on average, around a **40% mortality rate**. However, it remains a rare disease, especially in the West, with an incidence of approximately **1.7 – 6.2 cases per 100,000 patient years**.

Men are more commonly affected than women (ratio of **>2:1**), with higher rates seen in multimorbid patients, the elderly, those with internal cardiac devices and intravenous drug users.

Anatomy

The wall of the heart is divided into **three main layers**:

- An outer epicardium (connective tissue and fat)
- A middle muscular myocardium
- An inner endocardium

The endocardium is the heart's thin, **smooth interior lining** covering the heart valves. It comprises a specialised endothelium (similar to that in blood vessels) and connective tissue.

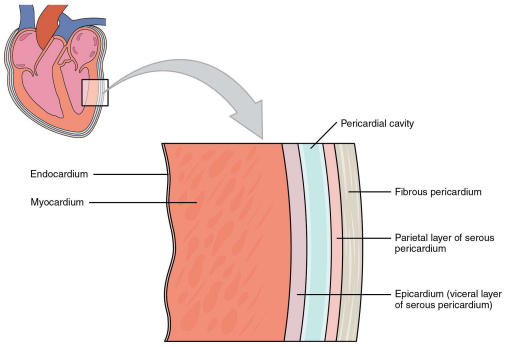


Figure 1. Layers of the heart wall.

Types of Endocarditis

- Infective Endocarditis
- Rheumatic Endocarditis
- Carcinoid Syndrome: *5-HT (serotonin) is produced in massive amount & its metabolites damage the endocardium especially right heart.*
- Marantic Endocarditis: *related with hypercoagulative state (formation of thrombi on valvular surface)*
- Systemic Lupus Erythematosus (Libman Sac Endocarditis)

Classification of Infective Endocarditis

Left Sided	Right Sided
– Mitral/aortic valve (most commonly involves)	– Tricuspid/pulmonary valve (5-10%)
Native Valve Endocarditis	**Prosthetic Valve Endocarditis**
– Patient's own heart valves are affected	– Bioprosthetic or mechanical valve are affected – **Prosthetic valve endocarditis** (PVE) makes up 20% of all endocarditis cases. This is the most severe form of endocarditis, and the prognosis is often poor.
Acute Infective Endocarditis	**Subacute Infective Endocarditis**
– Caused by highly virulent organism e.g., *Staphylococcus Aureus (gram +ve)*	– Usually Caused by **low virulent organism** e.g., *Streptococcus Viridans (gram +ve),* other gram -ve microbes like: *Hemophilus, Actinobacillus, Cardiobacterium, Eikenella corrodens, Kingenella kingae* **(found in oral cavity as commensals)**
– Occurs in healthy heart	– Person or heart is predisposed to pathological conditions (these factors are discussed further)
– Onset is stormy – High grade fever – Destructive lesions on heart develops rapidly	– Onset is insidious – Low grade fever – Destructive lesions on heart develops slowly with that there is always attempt for healing & fibrosis
– Cardiac specific complications & clinical features (leucocytosis etc.)	– Non-specific, general & constitutional or ill-defined features (anemia of chronic disease & leukopenia usually)
– If not treated patient will die within few weeks or days	– Patient not die early

Risk factors

Endocarditis risk factors may be divided into those related to the heart (**intrinsic**) and those external to the heart (**extrinsic**).

Intrinsic risk factors include:

- Valvular stenosis or regurgitation: congenital or acquired
- Hypertrophic cardiomyopathy
- Structural heart disease with turbulent flow (e.g. VSD, PDA): but **NOT** isolated ASD or fully repaired VSD or PDA
- Prosthetic heart valves: these will require replacement if infected
- Previous infection (infective endocarditis/rheumatic fever) causing structural damage

Extrinsic risk factors include:

- Intravenous drug use (right-sided endocarditis)
- Invasive vascular procedures (e.g., central lines)
- Poor oral hygiene/dental infections

Predisposing Factors

Abnormal Blood Flow:

- Injury to endocardium due to abnormal flow of blood can lead to formation of micro thrombi which helps to colonize bacteria with low virulence on thrombus (act as hiding place) & goes to deeper layers where they are well protected from the compliment system, antibodies, & inflammatory actions.

Valvular Conditions:

- Bicuspid aortic valve
- Calcific aortic valve
- Mitral Valve Prolapse with mid-systolic click followed by late systolic murmur (due to regurgitation) *this condition need prophylaxis*
- Prosthetic valve

Rheumatic Heart Disease

Host Factors: Playing a role in Acute as well as in subacute infective endocarditis

- Weak defenses against bacteria due to e.g., neutropenia, AIDS, malignancy, therapeutic immunosuppression (patient who have autoimmune disease taking steroids, cancer taking anticancer drugs or chemotherapy, liver transplant & to prevent immune related rejection)
- Diabetes Mellites
- Chronically alcoholic not taking balanced diet
- IV drug abusers develop infective endocarditis on right sided heart in tricuspid valve: these patients develop infective endocarditis due to polymicrobial activity.

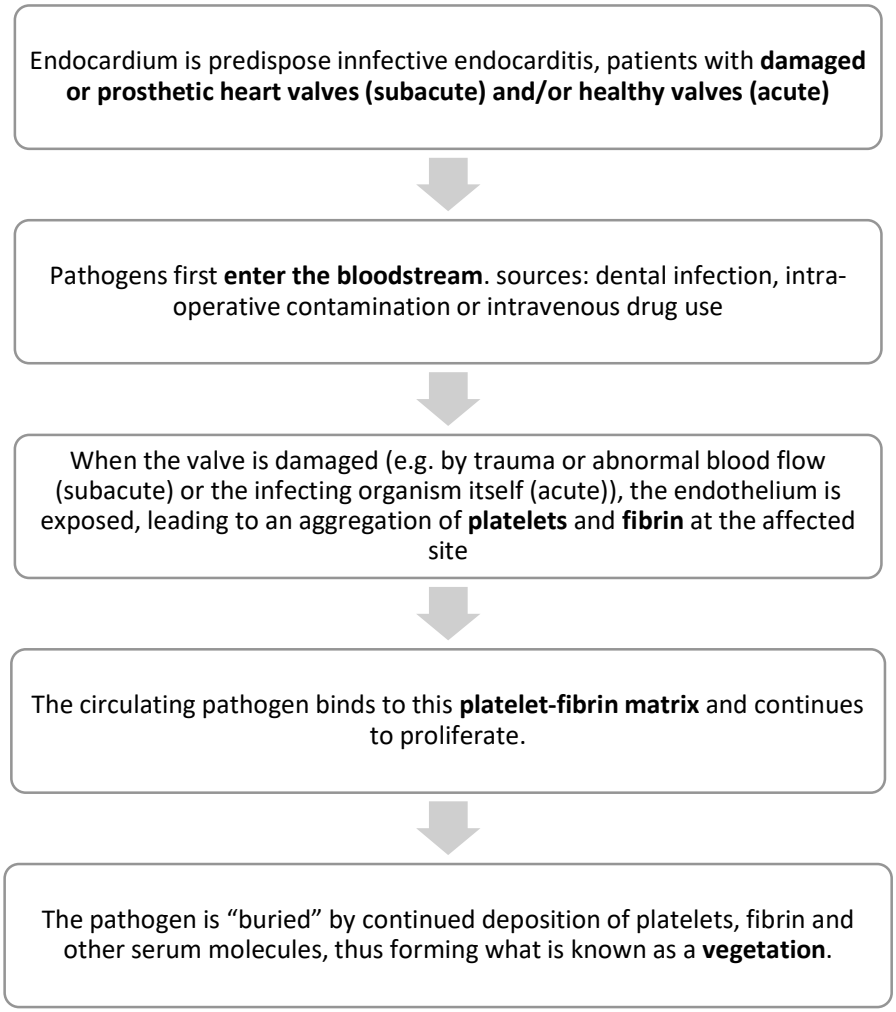
Do You Know?

Endothelium of circulatory vessels & endocardium of the heart is relatively resistant to thrombus formation & also relatively resistant to the colonization by microbes. If a person or a heart is predisposed to infective endocarditis then even an organism with low virulence can produce a disease.

Pathophysiology

Infective endocarditis arises from **three key factors** occurring simultaneously:

1. Transient bacteraemia
2. Damage to valvular tissue
3. Formation of vegetations



The pathogen is “buried” by continued deposition of platelets, fibrin and other serum molecules. This explains why removing the organism is difficult for the host immune system. In addition, the endocardium is **poorly vascularised** and difficult for antibiotics to penetrate, and prolonged courses of strong antibiotics are therefore required to clear the infection.

These vegetations have the potential to **embolise** and cause further complications. Emboli resulting from **left-sided** endocarditis may cause cerebral infarcts (strokes) or cerebral abscesses, whereas those from **right-sided** endocarditis may lead to mycotic aneurysms, pulmonary infarcts or pulmonary abscesses.

Deposition of circulating **immune complexes** in organs such as the skin, kidneys and eyes (an example of a type 3 hypersensitivity reaction) is also seen.

Aetiology & Microbiology

Bacteria cause most cases of endocarditis, with Staphylococci now overtaking Streptococci as the leading pathogen.

Table 1. Causative pathogens of infective endocarditis.

Class	Causative Organism
Gram Positive Bacteria	– Staphylococcus Aureus most common in acute infective endocarditis (IV drug abusers) – Streptococcus Viridans most common in subacute infective endocarditis – Staphylococcus Epidermides most common organism causing infective endocarditis in prosthetic valve in late time >3 months ~ **Early PVE** is seen within 12 months of surgery due to intraoperative contamination or spread to the valve via the blood within days or weeks of the operation. *Staphylococcus aureus* is most commonly associated with early PVE. These microbes are planted during surgery. ~ **Late PVE**, on the other hand, is a community-acquired infection that occurs more than 12 months post-op and is caused by similar microorganisms to those found in native valve endocarditis (streptococci, *Staphylococcus aureus*). – Most common organism coming from urogenital is Enterococci – Rare but extremely Important condition is when someone develops infective

	endocarditis from Streptococcus Bovis because it is found that the patient have malignant GIT e.g., colon carcinoma, ulcerative colitis
Gram Negative Bacteria	HACEK organisms* - **H**emophilus - **A**ctinobacillus - **C**ardiobacterium - **E**ikenella corrodens - **K**ingenella kingae Non-HACEK organisms - Pseudomonas aeruginosa - Neisseria elongata
Fungi	- Candida - Aspergillus Rarely develops fungal infective endocarditis. These patients need to manage surgically because the vegetations are very large & fungus is well protected in the centre of the vegetation.
Blood culture-negative infective endocarditis (BCNIE)	In a significant proportion of cases (up to 31%), no causative microorganism is identified from standard blood culture methods – so-called **blood culture-negative infective endocarditis** (BCNIE). This is often due to the patient receiving antibiotic therapy **before blood cultures** are taken. - HACEK - Coxiella burnetti (Q fever) - Bartonella spp (trench fever & cat-scratch disease) - Chlamydia spp

Still, there are several important bacteria to remember, as further investigations may be required to identify them (e.g. serology).

Diagnosis

Patients with infective endocarditis may present acutely (otherwise known as **fulminant endocarditis**) or subacutely over weeks to months.

History

Presentation is **variable**, but patients may complain of systemic features of **infection** (such as fever, malaise, night sweats, weight loss, anorexia) and symptoms of **anaemia** (such as fatigue and breathlessness).

Clinical examination

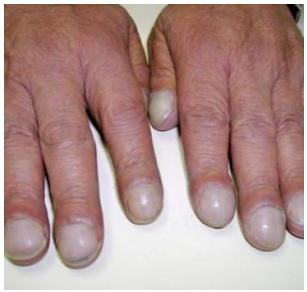
All patients with suspected infective endocarditis require a thorough **cardiovascular examination**.

Typical **clinical findings** in infective endocarditis include:

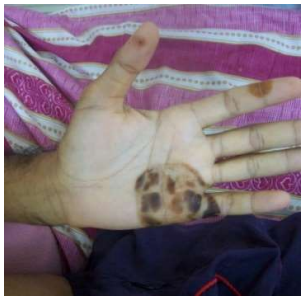
- Fever
- Tachycardia
- New or changing heart murmur
- Splinter haemorrhages: nailbed petechial haemorrhages
- Osler's nodes (**tender** subcutaneous nodules in the fingers) and Janeway lesions
- (**painless** erythematous macules on the palms): see Table 2
- Roth spots (boat-shaped retinal haemorrhages, pale in the centre)
- Clubbing: typically, a late sign
- Mild splenomegaly
- Bi-basal lung crepitations: heart failure in severe cases
- Patients may also present with clinical features from **emboli** (e.g. weakness from a stroke).

Table 2. Comparison between Osler's nodes and Janeway lesions

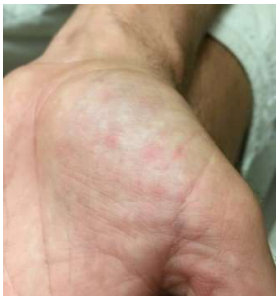
Osler's nodes	Janeway lesions
Painful (Osler's Ow!)	Painless
Typically affects fingers/toes	Typically affects palms/soles
Nodules	Macules/papules
Purple-pink with a pale centre	Erythematous/haemorrhagic
Localised immune-mediated response	Septic emboli
Subacute endocarditis	Acute endocarditis
Last hours to days	Last days to weeks



Finger clubbing: a late feature



Osler's Nodes



Janeway lesions

The “classical” stigmata should not be used to make the diagnosis alone as these are unreliable. Instead, diagnosis is based on the **duke criteria**.

Major Criteria	Minor Criteria
• Blood culture positive for infective endocarditis • Typical organism in 2 culture • Persistently positive blood culture ≥3 culture, 12 hours apart • Evidence of endocardial involvement • New valvular regurgitation • Vegetations • Intracardic absecess • New partial dehiscence of artifical valve from its anatomical position	• Predisposing factors • Intravenous drug abusre or predisposing heart condition • Temperature >38° C • **Vascular phenomemon**: includes major arterial emboli, septic emboli, pulmonary infarct, intracranial hemorrhage or **immunological phenomenon**: include glomerulonephritis, painful nodes, Roth's spots, splinter hemorrhage • ECHO findings: which are not qualifying the major criteria • Microbiological evidence: Positive blood culture not meeting a major or serologic evidence of an active infection with an organism known to cause infective endocarditis

Definitive Diagnosis

- 2 major criteria or 1 major criteria & 3 minor criteria or 5 minor criteria

Possible Diagnosis

- 1 major & 1 minor criteria or 3 minor criteria

Rejected endocarditis

A diagnosis of endocarditis is **rejected** when there is:

- A firm alternative diagnosis or
- Sustained symptom resolution after <4 days of antibiotics

Positive blood cultures.

These must meet **ONE** of the following criteria:

Positive for typical microorganisms on two or more separate occasions including *Strep viridans, Strep bovis,* HACEK group, *Staph aureus,* Community-acquired enterococci (in the absence of a primary focus).

Persistently positive cultures for microorganisms consistent with IE: ≥2 positive blood cultures of blood samples drawn >12 h apart **or** all of 3 or a majority of ≥4 separate cultures of blood (with first and last samples drawn ≥1 h apart).

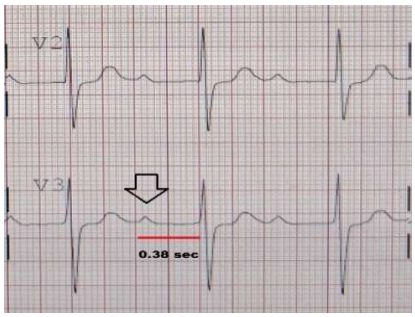
A single positive culture for *Coxiella burnetti* or high antibody titre (>1:800)

Other Investigations

Bedside investigations

Relevant **bedside investigations** include:

- **Basic observations (vital signs)**: signs of infection (fever, tachycardia).
- **12-lead ECG**: to exclude first degree AV block (Figure 1). This may be seen in aortic root abscesses, which are a rare complication of infective endocarditis.
- **Urine dipstick**: microscopic haematuria.



Prolongation of the PR interval, indicating first degree AV block. This may be a sign of aortic root abscess, a rare complication of endocarditis.

Laboratory investigations

Blood cultures

Blood cultures are a key part of the workup for endocarditis and should ideally be obtained **before starting antibiotic therapy**. This will reduce the number of negative cultures and help to guide appropriate treatment.

The European Society of Cardiology (ESC) recommends that **three sets** of blood cultures (i.e. **six bottles** in total) be taken, at least 30 mins apart, from three separate peripheral sites. A minimum of 10 ml of blood per bottle should be collected. Preferably when the fever is at peak.

Other laboratory investigations

Other relevant **laboratory investigations** include:

- **Full blood count**: to exclude anaemia (↓Hb) and check white cell count (WCC) to track the progress of the infection and response to treatment.
- **CRP/ESR**: inflammatory markers, used together with WCC (CRP more so). CRP may lag slightly behind WCC.
- **Urea & electrolytes**: baseline renal function and creatinine clearance is required if starting on nephrotoxic antibiotics such as gentamicin.

Differential diagnoses

Important differential diagnoses can be divided into autoimmune/rheumatological, infective and neoplastic.

Autoimmune/rheumatological differential diagnoses to consider include:

- Systemic lupus erythematosus: may present with non-infective (Libman-Sacks) endocarditis
- Antiphospholipid syndrome: thromboemboli, cardiac valve disease
- Vasculitis
- Polymyalgia rheumatica: myalgia, raised inflammatory markers
  Reactive arthritis

Infective differential diagnoses to consider include:

- Lyme disease: fever, myocarditis (rarely)
- Meningitis: fever, rash
- Tuberculosis: fever, night sweats, weight loss

Neoplastic differential diagnoses to consider include:

- Atrial myxoma: fever, new murmur (“tumour plop”, mid-diastolic rumble)

Complications

Infective endocarditis can cause localised and systemic complications.

Localised complications include:

- Valve destruction
- Heart failure (secondary to valve regurgitation)
- Arrhythmias and conduction disorders (e.g. AV block)
- Myocardial infarction
- Pericarditis
- Aortic root abscess

Systemic complications include:

- Emboli (e.g. stroke, splenic infarction)
- Immune complex deposition (e.g. glomerulonephritis)
- Septicaemia
- Death

Imaging investigations

Transthoracic echocardiogram (65% specificity) is the **first-line imaging investigation** in endocarditis and should be performed as soon the diagnosis of endocarditis is suspected. Note that not all vegetations are picked up on echocardiogram.

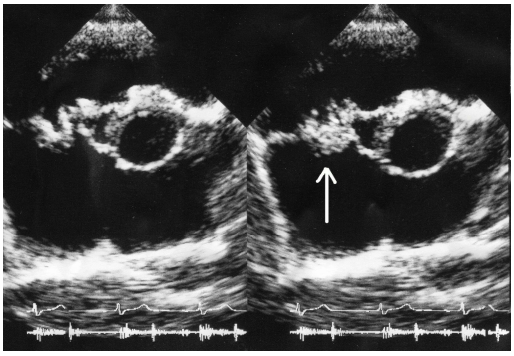


Figure 6. Vegetation on tricuspid valve visualised on echocardiography. Arrow denotes the vegetation.

Other relevant **imaging investigations** include:

- **Transoesophageal echocardiogram (95% specificity)**: more invasive but provides more detail than TTE. It can aid in diagnosis where endocarditis is clinically suspected but initial TTE is negative. It may also be used to rule out local complications in patients with a positive initial TTE.
- **Chest X-ray**: may be requested as part of the initial infection screen where the diagnosis is unclear. It may also be requested when heart failure (a serious complication of endocarditis) is suspected.
- **CT chest**: this can be helpful if a root abscess is present and if the patient is considered for surgery. When planning a re-do-sternotomy for prosthetic endocarditis, a pre-operative CT will be required as the heart structures may be stuck to the sternum.

Management

- ## Medical management

  The mainstay of treatment of infective endocarditis is **prolonged courses of antibiotics** (or antifungals if the infection is of fungal aetiology). Antibiotics are initially given **intravenously** for at least **two weeks** before switching to oral preparations.
  The European Society of Cardiology (ESC) advises that treatment should last for at least **six weeks** in patients with **prosthetic** valves and **two to six weeks** for **native** valve endocarditis.

The start of the antibiotic course is taken from the first day a **negative set of blood cultures** is obtained (even though antibiotics will have been given before this).

The choice of antibiotic regimen depends on **multiple factors** including previous antibiotic use, the type of valve affected (native vs prosthetic), the microorganism involved and the antibiotic sensitivity of the particular organism.

- **Surgical management**

  Occasionally, antibiotics alone may not be enough to treat the infection and surgery to **repair or replace** the valve may be required.
  Every patient with prosthetic valve endocarditis should have an urgent surgical review.
  Indications for surgery include:
  - Heart failure (i.e., severe valve disease, pulmonary oedema or cardiogenic shock)
  - Uncontrolled infection
  - Prevention of embolism (large vegetations)

Prophylaxis

Patients at **risk of endocarditis** may have other unrelated medical conditions requiring intervention.

Cardiac Conditions Associated with the Highest Risk of Adverse Outcome from Endocarditis for Which Prophylaxis with Dental Procedures Is Reasonable

Prosthetic cardiac valve or prosthetic material used for cardiac valve repair
Previous IE
Congenital heart disease (CHD)*
– Unrepaired cyanotic CHD, including palliative shunts and conduits
– Completely repaired congenital heart defect with prosthetic material or device, whether placed by surgery or by catheter intervention, during the first 6 months after the procedure†
– Repaired CHD with residual defects at the site or adjacent to the site of a prosthetic patch or prosthetic device (which inhibit endothelialization)
Cardiac transplantation recipients who develop cardiac valvulopathy
*Except for the conditions listed above, antibiotic prophylaxis is no longer recommended for any other form of CHD. †Prophylaxis is reasonable because endothelialization of prosthetic material occurs within 6 months after the procedure.

Antibiotic Prophylactic Regimens for Dental Procedures

Regimen – Single dose 30 to 60 minutes before procedure

Situation	Agent	Adults	Children
Oral	Amoxicillin	2 g	50 mg/kg
Unable to take oral medication	Ampicillin **OR**	2 g IM or IV	50 mg/kg IM or IV
	Cefazolin or ceftriaxone	1 g IM or IV	50 mg/kg IM or IV
Allergic to penicillins or ampicillin—oral regimen	Cephalexin*	2 g	50 mg/kg
	OR		
	Azithromycin or clarithromycin	500 mg	15 mg/kg
	OR		
	Doxycycline	100 mg	<45 kg, 2.2 mg/kg >45 kg, 100 mg
Allergic to penicillin or ampicillin and unable to take oral medication	Cefazolin or ceftriaxone†	1 g IM or IV	50 mg/kg IM or IV

Clindamycin is no longer recommended for antibiotic prophylaxis for a dental procedure.

IM indicates intramuscular; and IV, intravenous.

* Or other first- or second-generation oral cephalosporin in equivalent adult or pediatric dosing.

† Cephalosporins should not be used in an individual with a history of anaphylaxis, angioedema, or urticaria with penicillin or ampicillin.

Prognosis

the prognosis of infective endocarditis is variable and depends on many factors

- Early Diagnosis and Treatment
- Type of Organism (*Staphylococcus aureus* are associated with a higher mortality rate compared to those caused by *Streptococcus viridans*)
- Heart Valves Involved (native or prosthetic valve)
- Complications
- Surgical Intervention
- Underlying Health Conditions
- Mortality Rate
- Recurrence.

With timely and appropriate medical and sometimes surgical treatment, many patients can recover, but the condition remains serious with a significant risk of complications and mortality. Regular follow-up and monitoring are crucial to manage long-term outcomes effectively.

What is vegetation

Vegetation is a morphologically typical pathological lesions of the infective endocarditis

Difference between acute & subacute vegetations in infective endocarditis

Vegetations in Acute Infective Endocarditis:

1. **Highly virulent organism sticks** to the healthy endocardium, colonize & invade the endocardium
2. Heavily damage the endocardium
3. **Platelets & fibrins** are start attaching to damaged endocardium
4. **Inflammatory reactions** occur, **WBCs reached** at damaged site
5. **Multiple colonies of microbes** grow with time
6. More platelet, fibers, ↑↑↑ Microbes, ↑↑↑ inflammatory cells (Neutrophils/macrophage, Monocytes, Lymphocytes)
7. Lots of **proteolytic substances** (destructive enzymes) **released**, leads to very **rapid & aggressive destructive vegetations** (large, friable vegetations are produced) they can ulcerate or even perforate the valve
8. These vegetations can breaks into pieces, can **embolize (systemic embolization)**, patient start developing **metastatic abscess** (pocket of pus)
9. If the vegetations starts on the valve ring they can move around the ring (because fibrous annulus on valvular ring is not resistant to infection), causes **ring abscess** if it is **around aortic valve ring can fail conduction system (prolonged PR interval)**, if it is **around prosthetic valve**, it **can dehiscence** (separation of the valve tissue) from its anatomical position, if reach **to the myocardium can leads to myocardial abscess**, if **in pericardial layer leads to suppurative pericarditis**

Vegetations in Subacute Infective Endocarditis

1. Low virulent organism in predisposed heart leads to subacute infective endocarditis
2. Other mechanism is same as in acute phase except this in inflammatory reaction less neutrophils but more macrophages with lymphocytes, vegetations held tightly (less prone to embolization) & disease is running from weeks to months thus these patients develop chronic antigenemia (bacteria keep on releasing antigens in circulation)
3. Antigen-antibody complexes are formed in circulation (immune complexes are formed)
4. **Type 3 Hypersensitivity Reaction** & Immune complexes deposit into micro circulation & damage the local area by complements causing vasculitic lesions
    - If immune complexes deposit in the fingers under the nail's capillaries develop vasculitic/haemorrhagic – elongated/liner/flame shaped lesions called **Splinter haemorrhage**.
    - Inflammatory painful lesions under finger tips called **Osler nodes**
    - Destructive lesions in the palms, palmer aspect or planter aspect of the foot may be found in skin – non tender, red spot (called petechial haemorrhage) may develop called **Janeway's lesions**
    - Similar lesions (Janeway's lesions) may form in retina as circular board shaped haemorrhagic lesions with pale yellow centres called **Roth spots**
    - If immune complexes deposit in glomeruli **diffuse glomerulonephritis** may develop (because in both kidneys all glomeruli are inflamed) patient may develop proteinuria & hematuria in severe case renal failure (more commonly in acute-type)
    - If immune complexes deposit in pleural membrane → **pleuritic rub & pain** may occur, if in pericardial membrane → **pericardial rub** may occur
    - If immune complexes deposit in synovial membrane can develops **polyarthritis (feature of chronic immune complex disease)**