Infective endocarditis

Objectives:

- Understand the definition of Endocarditis
- Know the patho-physiology of endocarditis
- Know the presentation of patients with endocarditis
- Know the treatment of endocarditis
- Know the ways to prevent endocarditis

[Color index : Important | Notes | Extra]

Resources:

- 435 slides

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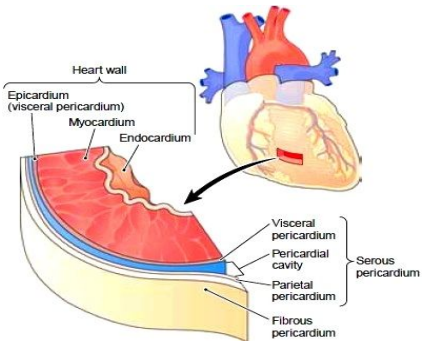
Infective Endocarditis



- **Review:** The heart wall is composed of three layers which includes:
  1. **Innermost layer:** endocardium (Inflammation = Endocarditis)
  2. **Middle layer:** myocardium (Inflammation = Myocarditis)
  3. **External layer:** epicardium (Inflammation = Pericarditis)
- **Definition:**

***Infective endocarditis* is an infection of the endothelial surface of the heart in:**

- ➔ **Heart valves** (usually involves cusps of valves & intracardiac foreign bodies, such as *prosthetic valves, pacemaker leads and surgical conduits*[1]).
- ➔ **Septal defects**[2]
- ➔ **Chordae Tendinea**
- ➔ **Arteriovenous shunt**[3]

★ Normal healthy people will never have endocarditis, so who will get EI? The one who has a problem in his endocardium like VHD, congenital heart disease or having a prosthetic valve.

★ It remains a life-threatening disease with significant mortality (about 20%) and morbidity.

- **Pathogenesis:** What is the pathogenesis of EI?
  - ➔ IE is the net result of the **complex interaction** between the bloodstream pathogen with matrix molecules and platelets *at sites of endocardial cells damage*.

1. **Endothelial Damage**	Caused by **turbulent blood flow** produced by either a congenital or acquired heart disease (such as flow from a high- to a low-pressure chamber or across a narrowed orifice of high velocity. *"Valvular lesions may create non-laminar flow, and jet lesions from **septal defects** or a patent ductus arteriosus result in abnormal vascular endothelium"*. Turbulence : High pressure > Lower pressure > injury to endocardium (In diseased endocardium, turbulent blood flow will lead to trauma to that endocardium this trauma will create matrix molecules (WBCs,inflammatory agents, antigen-antibody reaction) adding to it platelets > they will integrate at the site of the trauma > They will form Vegetations .
2. **Formation of Non-Bacterial Thrombotic Endocarditis (NBTE)**	Caused by the **deposition of platelets and fibrin** on the surface of the endothelium which was facilitated by the endothelial damage.
3. **Trauma to a mucosal surface heavily populated by endogenous microflora**	Such as the gingiva around the **teeth, oro-pharynx**, GI Tract, urethra and vagina. Nowadays it's mostly the oral mucosa. Any gingival or dental manipulation leading to trauma of mucosal surfaces of the mouth is a source of IE (bacteria enter the blood > heart > combine with vegetations) FOR PERSON SUSCEPTIBLE TO ENDOCARDIUM PROBLEMS (VHD,prosthetic valve or congenital heart disease). • Role of GI Tract, urethra and vagina in IE is controversial
4. **Transient Bacteremia**	Bacteraemia may arise for **patient-specific reasons** (poor dental hygiene, intravenous drug use, soft tissue infections) or **may be associated with diagnostic or therapeutic**

[1] Apicoaortic Conduit (AAC), also known as Aortic Valve Bypass (AVB), is a cardiothoracic surgical procedure that alleviates symptoms caused by blood flow obstruction from the left ventricle of the heart. Picture

[2] Heart septal defect refers to a congenital heart defect of one of the septa of the heart (Atrial septal defect, Atrioventricular septal defect, Ventricular septal defect).

[3] An arteriovenous fistula is an abnormal connection or passageway between an artery and a vein.It may be congenital, surgically created for hemodialysis treatments, or acquired due to pathologic process, such as trauma or erosion of an arterial aneurysm.

	procedures (dental treatment, intravascular cannulae, cardiac surgery or permanent pacemakers).
5. **Bacterial Adherence:** Microorganism adherence (BTE)	Damaged endocardium promotes platelet and fibrin deposition(NBTE), which allows organisms to adhere and grow, leading to an **infected vegetation**[4]**.**This will result in the proliferation of bacteria within a vegetation and will hence form IE. (Local vegetation,Extension, Perivalvular ,Destructive valve, fistula and embolization).

- ***Note : .Aortic and mitral valves are most commonly involved in infective endocarditis; intravenous drug users are the exception, as right-sided lesions are more common in them.***

Risk Factors:

The risk is determined based on:

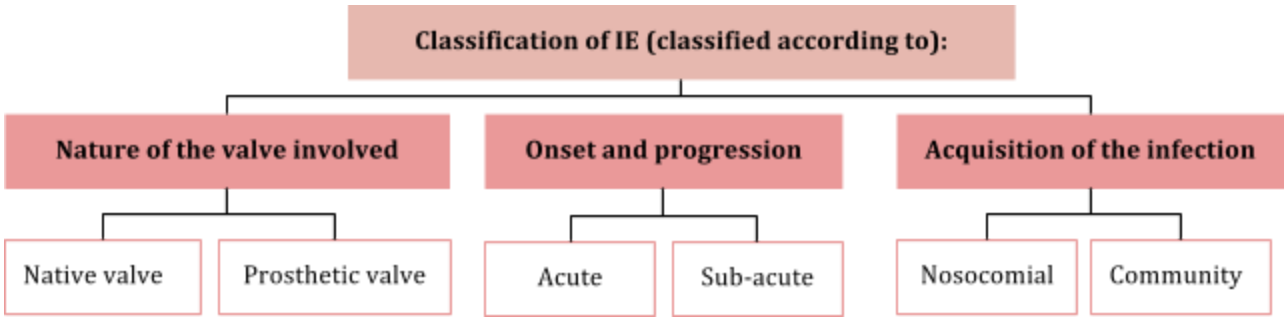
- ➔ *The presence or absence of a cardiac condition*
- ➔ *The type of procedure to be done* dental procedure have very high risk and could lead to IE in previously ill patient (VHD,prosthetic valve or congenital heart disease).

Based on the risk of progression to severe endocarditis with substantial morbidity and mortality, IE is classified into:

High risk: (Needs Prophylaxis)	Low risk: (Does NOT need Prophylaxis)
Give prophylaxis if the patient: • is undergoing a **Dental procedure** (as there is risk of bacteremia). According to ACC 2017 guidelines, only dental procedures that involve the manipulation of gingival tissue, periapical region of the teeth, and perforation of the oral mucosa are the ones that require prophylaxis. • has: - Prosthetic valves including trans-catheter-implanted prostheses & homografts. - Prosthetic material used for cardiac valve repair, such as annuloplasty rings & chords. - History of previous endocarditis - Congenital heart defect such as Complex cyanotic disease (Tetralogy, Transposition, Single Ventricle), Patent Ductus Arteriosus, VSD and Coarctation of aorta. - Unrepaired cyanotic congenital heart disease or repaired congenital heart disease, with residual shunts or valvular regurgitation at the site of or adjacent to the site of a prosthetic patch or prosthetic device. - Cardiac transplant with valve regurgitation due to a structurally abnormal valve.	• Acquired Valvular heart disease with stenosis or regurgitation. • Hypertrophic cardiomyopathy. • IV drug abuser. • Respiratory Tract procedures. • GIT or urogenital procedures. • Skin and soft tissue procedures.

[4] Vegetation complexes cause 2 major problems :
- Antigen-antibody reaction = Immune complex = EI can be immunologically mediated disease. Which could produce rash, glomerulonephritis, hematuria, Osler's nodes.
- It could be vascular (these vegetations may be distributed anywhere through the vasculature). May be dislodged and go to the brain > mycotic aneurysm/ stroke or it will go to the periphery and cause infarction anywhere.

Classification of IE:



- Which one is more risky native or prosthetic valve? Answer is prosthetic, because it is a metal so there is no blood supply and blood cannot reach it. Thus, antibiotics cannot reach there also. If you have a patient with prosthetic valve & EI there is no solution other than removing of that prosthetic valve.
- Acute & Subacute :

Acute:
- Most commonly by **Staph. Aureus**
- Occurs in a normal heart valve
- If untreated, fatal in less than 6 weeks

Subacute:
- Caused by less virulent organisms, e.g. **Streptococcus viridans** and Enterococcus
- Occurs on damaged heart valves
- If untreated, Takes much longer than 6 weeks to cause death

Clinical Features:

The clinical presentation of infective endocarditis is dependent on the organism and the presence of predisposing cardiac conditions. Infective endocarditis may occur as an acute, fulminating infection but also as a chronic or subacute illness with low-grade fever and nonspecific symptoms.A high index of clinical suspicion is required to identify patients with infective endocarditis and certain criteria should alert the physician.

A) High clinical suspicion

- **New valve lesion/(regurgitant) murmur.**
- **Embolic event(s) of unknown origin.**
- **Sepsis of unknown origin.**
- **Haematuria, glomerulonephritis and suspected renal infarction.**
- **'Fever' plus:**

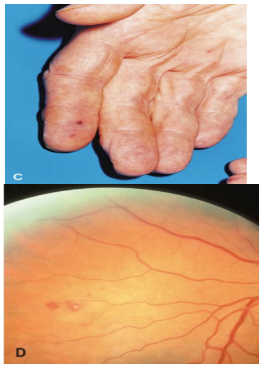
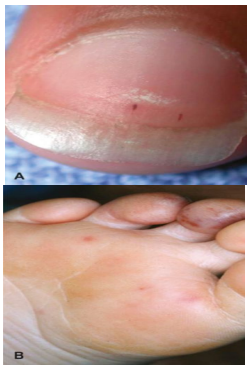
- Prosthetic material inside the heart
- Other high predisposition for infective endocarditis, e.g. intravenous drug use
- Newly developed ventricular arrhythmias or conduction disturbances
- First manifestation of congestive cardiac failure
- Positive blood cultures (with typical organism)
- Cutaneous (Osler, Janeway) or ophthalmic (Roth) lesions
- Peripheral abscesses (renal, splenic, spine) of unknown origin
- Predisposition and recent diagnostic/therapeutic interventions known to result in significant bacteraemia.

B) Low clinical suspicion (Fever plus none of the mentioned above).

Clinical features of infective endocarditis

Clinical feature	Approximate %
General	
Malaise	95
Clubbing	10
Cardiac	
Murmurs	90
Cardiac failure	50
Arthralgia	25
Pyrexia	90
Skin lesions	
Osler nodes	15
Splinter haemorrhages	10
Janeway lesions	5
Petechiae	50
Eyes	
Roth spots	5
Conjunctival splinter haemorrhages	Rare
Splenomegaly	40
Neurological	
Cerebral emboli	20
Mycotic aneurysm	10
Renal	
Haematuria	70

- **The onset is usually within 2 weeks of infection :**

<table>
<tr><td>Indolent course</td><td colspan="2">• fever, malaise, fatigue, night sweats, anorexia and weight loss. It is infective so, there will be fever, fatigue, malaise, lethargy, poor appetite and loss of weight (Constitutional Sx).</td></tr>
<tr><td>Explosive course</td><td colspan="2">• Congestive cardiac failure (CCF), new/changing murmur with severe systemic sepsis
Local destruction : vegetation complexes will cause damage to tissues which will result in mitral regurgitation, AR, papillary muscle destruction,..etc.</td></tr>
<tr><td rowspan="3">Other clinical features</td><td>Immunological manifestations</td><td>★ Osler's Nodes: painful, red, raised lesions found on the distal hands and feet "PIC C"
★ Roth Spots "PIC D"(retinal hemorrhages with white or pale centers)
★ Glomerulonephritis due to embolization to kidney
★ +ve Rheumatoid Factor[5]
- Once you're suspecting IE, look for : Splinter hemorrhage, osler's node and roth spots.
  </td></tr>
<tr><td>Vascular and septic emboli</td><td>★ Splinter Haemorrhages. "PIC A"
★ Musculoskeletal (arthritis).
★ Janeway Lesion[6]: painless hemorrhagic skin lesion in the palm and sole "PIC B"
★ Sub-conjunctival Hemorrhage
★ Mycotic Aneurysm embolization to Brain > stroke
★ Arthritis
★ Hematuria embolization to kidney
  </td></tr>
<tr><td>Others</td><td>• Splenomegaly
• Petechiae (conjunctival, buccal mucosa, palate & skin in supraclavicular area). Petechiae = bleeding under the mucus</td></tr>
</table>

(Mnemonic for the signs & symptoms of IE : FROM JANE)

[5] High levels of rheumatoid factor in the blood are most often associated with autoimmune diseases, such as rheumatoid arthritis and Sjogren's syndrome.

[6] Janeway lesions are one of the stigmata of infective endocarditis. They are irregular, erythematous, flat, painless macules on the palms, soles, thenar and hypothenar eminences of the hands, tips of the fingers, and plantar surfaces of the toes; they rarely present as a diffuse rash, and are very rare in clinical practice.

- ## Investigation:

  - ➔ **C.B.C** for leukocytosis or anemia (anemia because of hematuria and bleeding under the skin and eyes)
  - ➔ **ESR** High
  - ➔ **Blood cultures** +ve for suspected organisms
  - ➔ **Renal Function** Because there could be glomerulonephritis (one of the immunological manifestations)
  - ➔ **Urinalysis** for hematuria or bacteriuria
  - ➔ **ECG** for conduction defects
  - ➔ **Chest X-ray** for septic abscess in the lung secondary to embolization
  - ★ **Echocardiogram :** HALLMARK for vegetations. If TTE does not detect it, we can do TEE

- ## Causative Organisms of IE:

Native Valve Endocarditis	IV-Drug Abusers	Prosthetic Valve Endocarditis
1. **Streptococci: Viridans streptococci (50 - 70%).** 2. **Staphylococci:** Mostly Coagulase +ve **Staph. Aureus** Or Staph. Epidermidis **(25%)** 3. **Enterococci (10%)** 4. **HACEK:** Treatment: ceftriaxone - Haemophilus species - Actinobacillus - Actinomycetemcomitans - Cardiobacterium hominis - Eikenella - Kingella	- **Skin is the most predominant source of infection** - **70 - 100% of Right sided IE results in pneumonia and septic emboli** ★ **Staph aureus (because it's on the skin) 60%** 2. Streptococci and Enterococci (20%) 3. Gram -ve bacilli (10%) 4. Fungi (Candida and Aspergillus (5%) If a YOUNG man comes to you with fulminant endocarditis, SUSPECT DRUG ABUSE !! then check for an evidence. There may be NO underlying cardiac condition. **Staphylococcus** aureus is the causative organism in drug abusers. 70-100% will have septic embolization and pneumonia.	A. **Early onset: within 60 days after surgery** • Reflects perioperative contamination • Incidence around 1% • **Microbiology :** ➔ **Staph (45 - 50%)** **•Staph. Epiderm (30%)** **•Staph. Aureus (20%)** 2. Gram -ve aerobes (20%) 3. Fungi (10%) 4. Strep and Entero (5-10%) **B. Late onset: more than 60 days after surgery** • After endothelialization • Incidence 0.2 -0.5 % / pt. year • Transient bacteraemia from dental, GI or GU • Microbiology : – resembles native valve endocarditis ➔ **Streptococci**

★ IE MOST COMMON causative organism : **Streptococcus** viridans

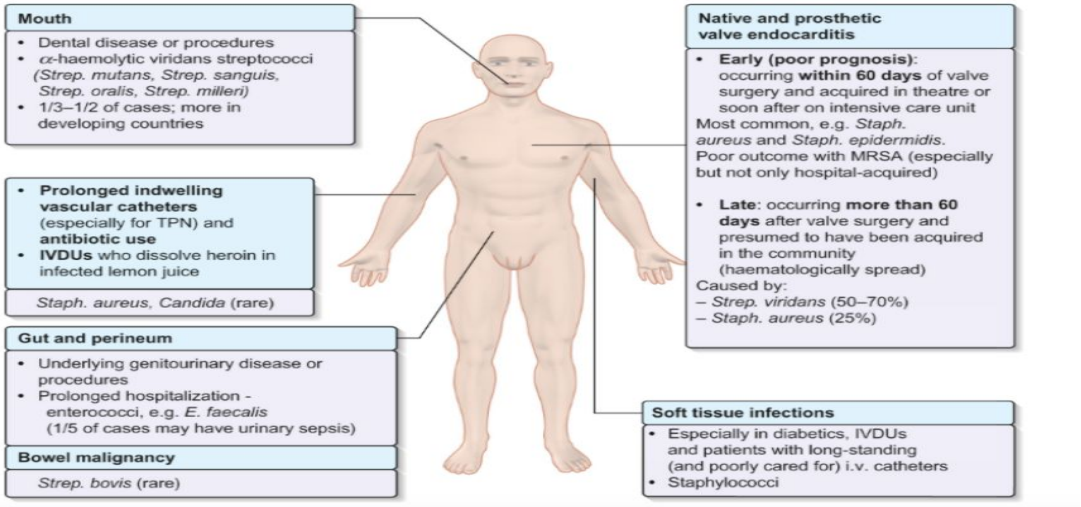
★ If a patient went through a cardiac surgery then he got infected with IE think about the period of time**, if it happened within 60 days after surgery then it is STAPH, if more than 60 days then it is STREPTOCOCCUS viridans.**[7]

★ **Staphylococcus aureus : 1) Drug abusers. 2) Immediate postoperative period.**

[7] الدكتور قال هذي موضع سؤال في الاختبار.

CULTURE-NEGATIVE ENDOCARDITIS

This accounts for 5–10% of endocarditis cases. The usual cause of this condition is prior antibiotic therapy . However, some cases are due to a variety of fastidious organisms that fail to grow in normal blood cultures. These include Coxiella burnetii (the cause of Q fever), Chlamydia species, Bartonella species (organisms that cause trench fever and cat scratch disease) and Legionella.



- **Diagnosis of IE:**

Major Criteria

1-Blood Culture positive for IE:

BE-FEVEER

B Blood Culture +ve
E ENDOCARDIAL INVOLVEMENT
F FEVER
V VASCULAR PHENOMINA
EE EVIDENCE FROM MICROBIAL
R RISK FCTOR FOR IE VALVE DISEASE

➔ **Typical microorganisms consistent with IE from 2 separate blood cultures**
- viridans streptococci, streptococcus gallolyticus (S. bovis), HACEK, staphylococcus aureus ;or
- Community acquired enterococci in the absence of a primary focus ;or

➔ **Microorganisms consistent with IE from persistently positive blood cultures**
- ≥2 positive blood samples drawn >12 hrs apart
- All of 3 or a majority of ≥4 separate cultures of blood (With first and last samples drawn ≥1 hour apart); or

➔ **Single positive culture for coxiella burnetii or phase I IgG antibody titre > 1:800**

2-Imaging positive for IE:

➔ **Echocardiogram positive for IE:**
- Vegetation
- Abscess , pseudoaneurysm ,intracardiac fistula
- Valvular perforation or aneurysm
- New partial dehiscence (a previously closed wound reopening) of prosthetic valve.

➔ **Abnormal activity around the site of prosthetic valve implantation detected by F-FDG PET/ CT (only if the prosthesis was implanted for > 3 months) or radiolabelled leukocytosis SPECT/CT.**

➔ **Definite paravalvular lesion by cardiac CT.**

Minor Criteria

1-Predisposition: such as predisposing heart condition or injection drug use

2-Fever : defined as temperature> 38 c

3-Vascular Phenomena (including those detected only by imaging): major arterial emboli , septic pulmonary infarcts , infectious (mycotic) aneurysm , intracranial hemorrhage , conjunctival hemorrhage and janeway's lesions.

4-Immunological Phenomena : glomerulonephritis , osler's nodes , Roth's spots and Rheumatoid factor.

5-Microbiological evidence : Positive blood culture but doesn't meet a major criterion or serological evidence of active infection with organism consistent with IE.

Diagnostic (Duke) Criteria 2015 :

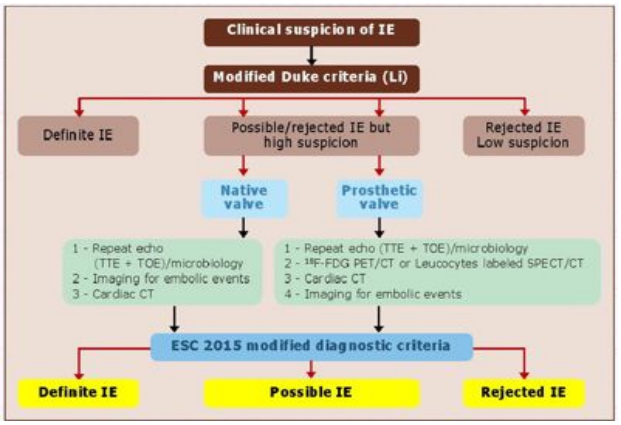
1. Definitive infective endocarditis:

A. Pathologic criteria

Microorganisms or pathologic lesions: demonstrated by culture or histology in a vegetation, or in a vegetation that has embolized, or in an intracardiac abscess.

B. Clinical criteria

Either 2 major criteria , **1 major and 3 minor** criteria or **5 minor criteria.**



2. Possible infective endocarditis:

- Findings consistent of IE that fall short of "definite", but not "rejected"
- IE considered in presence of **1 major and 1 minor** or **3 minor criteria**

3. Rejected infective endocarditis:

- Firm alternate Dx for manifestation of IE
- Resolution of manifestations of IE, with antibiotic therapy for ≤ 4 days
- No pathologic evidence of IE at surgery or autopsy, after antibiotic therapy for ≤ 4 days.

• Treatment [8]:

❖ Medical :

Principles of Medical Management :

Treat Vegetations with antibiotics: prolonged *(4–6 weeks),* high dose, and bactericidal (NOT BACTERIOSTATIC)

- **Acute onset:** blood culture and start treatment within three **hours**.
- **Subacute onset :** Blood culture then antibiotic can be started within three **days**.

The best initial empiric therapy is vancomycin and gentamicin.

Treatment of resistant Organism : Add an aminoglycoside and extend the duration of treatment.

Highly Penicillin susceptible streptococci viridans or bovis :

➔ Once daily **ceftriaxone** (or i.v. penicillin G or i.v. amoxicillin) for 4 weeks *(cure rate>98%)*

➔ Once-daily **ceftriaxone** 2 g for 2wks followed by oral amoxicillin for 2 weeks.

➔ Prosthetic valve may need longer treatment durations (continue if there is a response).

➔ ***In b-lactam allergic patients: Vancomycin***

Methicillin susceptible Staphylococcus :

Flucloxacillin[9] , In b-lactam allergic patients: Vancomycin.

★ Staph? Flucloxacillin Or Vancomycin (in case of there is allergy or no response). Strept? Penicillin Or Vancomycin.

❖ Surgical:

Indications for surgery : 1-Prosthetic valve 2-Big Vegetation. 3-Embolization (recurrent while on antibiotics) 4-**CHF or Ruptured valve** (strongest indication for surgery) or Chordae Tendineae 5-Fungal Endocarditis 6-Abscess 7-AV block Followed by 6 weeks of antibiotics.

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[8] Treatment : either medical or surgical,

- Surgical if there is a prosthetic valve (won't respond to medications because it is metal), if the vegetations are too big to be absorbed, or if the patient manifests with vascular phenomena(Embolization).
- Medical therapy is given to ALL patients even for those who will do a surgery because we need to eradicate the infection from the body. GIVE BACTERICIDAL NOT BACTERIOSTATIC !!!

[9] Unlike other penicillins, flucloxacillin has activity against beta-lactamase-producing organisms such as Staphylococcus aureus as it is beta-lactamase stable.

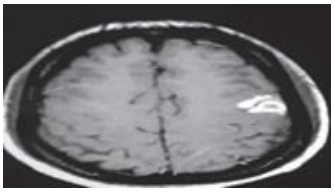
- **Main principles of prevention in IE:** Main principle of **p**revention : **p**rophylaxis and **p**recaution.
  1. The principle of antibiotic prophylaxis when performing procedures at risk of IE in patients with predisposing cardiac conditions is maintained.
  2. **Antibiotic prophylaxis must be limited to patients with highest risk of IE undergoing the highest risk dental procedures.**
  3. Good oral hygiene and regular dental review are more important than antibiotic prophylaxis to reduce the risk of IE.
  4. Aseptic measures are mandatory during venous catheter manipulation and during any invasive procedures in order to reduce the rate of healthcare-associated IE.
  5. Whether the use of antibiotic prophylaxis is really associated with a change in the incidence of IE needs further investigations.

- **Prophylaxis :**

Two features are needed to establish the need for prophylaxis: Significant cardiac defect, Risk of bacteremia

For dental procedure at risk : Amoxicillin or Ampicillin (If Allergic to penicillin or ampicillin:Clindamycin).

- **Complications of IE:**

Congestive Cardiac Failure: **Most common complication**	**Neurological Manifestations: (1/3 cases)**
• Valve Destruction • Myocarditis • Coronary artery embolism and MI • Myocardial Abscesses	• Major embolism to MCA (Middle cerebral artery) territory (25%) • Mycotic Aneurysms (2 -10%) 
Metastatic infections	**Renal impairment (Glomerulonephritis)**
• **Right Sided vegetations:** - Lung abscesses - Pyothorax / Pyo-pneumothorax • **Left Sided vegetations:** - Pyogenic Meningitis - Splenic Abscesses - Pyelonephritis - Osteomyelitis	As a result of immunological phenomena.

After studying the lecture, make sure that you're able to answer the following questions :)

1- WHICH PATIENTS IS CANDIDATE FOR IE ?
2- WHAT IS THE PATHOPHYSIOLOGY OF IE ?
3- WHICH PATIENTS NEED PROPHYLAXIS FOR IE ?
4- WHAT IS THE DIAGNOSTIC CRITERIA FOR IE ?
5- WHAT ARE THE ORGANISMS COMMONLY CAUSING IE ?

Question from Master the Boards:

1-A man comes into the emergency department with fever and a murmur. Blood cultures grow Streptococcus bovis. Transthoracic echocardiography shows a vegetation.
What is the most appropriate next step in the management of this patient?
a. Colonoscopy
b. Transesophageal echocardiogram
c. CT of the abdomen
d. Repeat the blood cultures
e. Surgical valve replacement

Answer: A. Streptococcus bovis is associated with colonic pathology ranging from diver-ticuli to polyps to colon cancer. If strep bovis grows, perform colonoscopy. CT scan will not show diverticuli. There is no point in repeating the blood culture if it is already positive. Valve replacement is premature.

1) Patient came to hospital with right Sided vegetations which of the following complications will you expect to see ?

A. Lung abscesses

B. Pyogenic Meningitis

C. Osteomyelitis

2**) Which of the following is not considered as a risk of IE Hypertrophic cardio-myopathy**

A. Valve replacement

B. Previous CABG

C. Oral dental procedure

3) Which of the following is considered as a risk of IE?

A. Roth spots

B. Osler's Nodes C.Pure Mitral Stenosis D. fever

4) Which of the following is considered as a minor Duke Criteria?

A. Positive blood culture for coxiella brunetti B

B. New Valvular regurgitation

C. Oscillating intra cardiac mass

D. IV drug abuse

5) Pulmonary Stenosis considered as?

A. High risk procedure for Infective endocarditis

B. Intermediate risk procedure for Infective endocarditis

C. Low risk procedure for Infective endocarditis

D. No relation at all between the procedure and Infective endocarditis

6) The strongest indication for surgery in IE is:

A. Persistence of fever

B. Embolization of vegetations

C. Perivalvular invasive disease

7) The composition of vegetation includes:

A. Fibrin + Platelet

B. Platelet + Inflammatory cells + smooth muscle cells

C. Inflammatory cells + Fibrin + Platelet

D. lymphocyte + fibrin

8) Patient underwent a major surgery 3 weeks ago , came to hospital complaining of Fever , Fatigue and Osler's Nodes after investigation they diagnosed him with IE

What is the most likely organism ?

A. Viridans Streptococci

B. Haemophilus species

C. Enterococci

D. Staph. Aureus

9) the patient has 4 chamber dilatation with a left ventricular EF of 15% he has moderate mitral regurg and moderate tricuspid regurg, with an estimated pulmonary artery pressure of 70mm Hg. He has a moderate pleural effusion, elevated Liver Function Tests, hypokalemia and hypomagnesaemia, his bb is 115/60, HR 110 bpm, respiratory rate is 30, Oxygen saturation on room air is 88%, initial therapy should include all of the following except:

A. IV loop diuretics

B. Digoxin

C. ACE inhibitors

D. Beta blockers

10) A 28-year-old man with a history of intravenous drug abuse presents to the emergency department with a 2-day history of fever, chills, and shortness of breath. On physical examination the patient has a new heart murmur, small retinal hemorrhages, and subungual petechiae. Which of the following is the most likely causative organism?

A. Group A Streptococcus

B. Mycobacterium tuberculosis

C. Staphylococcus aureus

D. Staphylococcus epidermidis

E. Streptococcus viridans

1	2	3	4	5	6	7	8	9	10
a	c	c	d	b	b	c	d	d	c