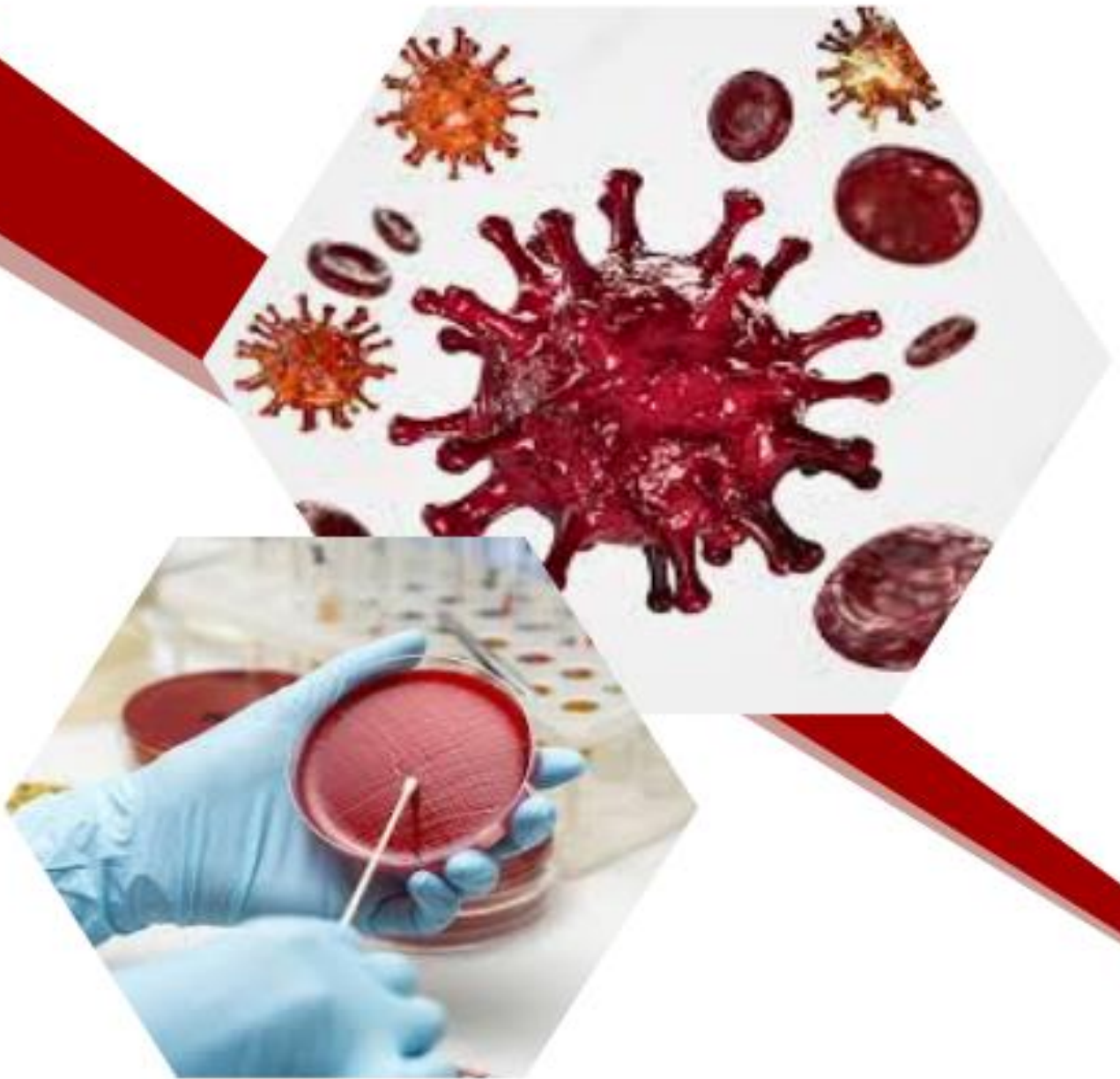


Doctor.021

no. 1

CVS MICROBIOLOGY



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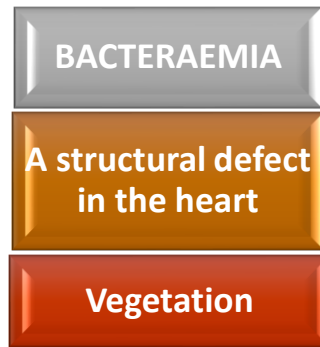
Infective endocarditis (IE)

- Its name used to be bacterial endocarditis, but they have changed it as it's not only caused by bacterial agents; fungi and viruses (even corona-virus and its vaccine) can also cause this disease.
- Infective endocarditis (IE) is an inflammation of the endocardium... inner of the heart muscle & the epithelial lining of heart valves.
- It is a rare, life-threatening disease that has long-lasting effects even among patients who survive and are cured.
- It is caused by damage to the endocardium of the heart followed by microbial, usually bacterial, colonization.
- Once established, IE can involve almost any organ system in the body and can be fatal if left untreated (whether acute or subacute).
- It is mostly a nosocomial infection (disease originating in hospitals); thus, as doctors, we should always be careful.
- It has diagnostic criteria called 'Modified Duke criteria'.
- Its prognosis is worse than all cancers. IEs one-year mortality rate is 30% even when treated.

Epidemiology

- The crude incidence ranged from 1 to 10 cases per 100,000 person-years.
- Rheumatic heart disease remains the key risk factor for infective endocarditis in low-income countries and underlies up to two-thirds of cases.
- In high income countries, However, degenerative valve disease, diabetes, cancer, intravenous drug use, and congenital heart disease have replaced rheumatic heart disease as the major risk factors for infective endocarditis.
- The mean age of patients with IE has increased significantly (past 50 years old).
- Untreated, mortality from IE is uniform. Even with best available therapy, contemporary mortality rates from IE are approximately 25%.

- We have 3 independent factors(prerequisites) that must be present for IE to happen; they don't necessarily occur in order though.



- Many daily activities such as tooth brushing or chewing gum can cause transient bacteraemia (the simple presence of bacteria in the blood) - it is different than septicemia which is blood poisoning due to the presence of bacteria.
- Years ago, rheumatic heart disease was the predisposing factor -the structural defect- in most people, but a shift in the epidemiology and age incidence occurred as it now affects older people and the ones with degenerative valvular disease.
- Vegetation: the bacteria adhere, multiply and colonize on heart valves; considered as bacteria+ leukocytes+ platelets+ fibrin clot and the vegetation might disseminate forming emboli or causing infarction.
- Rheumatic heart disease: caused by group A β -hemolytic streptococci that lead to strep throat/**strep pyogenes** or skin infections (impetigo) and infected patients can develop rheumatic heart disease 2-4 weeks later. It used to be a common presentation in young adolescents and so did IE.
- Remember that a shift in the age incidence happened and older people (>50) are now more susceptible – opposite to the age incidence in rheumatic heart disease; this is due to changes in predisposing factors like the increased life expectancy. Rheumatic heart disease is no longer the major cause of IE especially in developed countries.
- Degenerative valvular diseases are now the major causes, as well as invasive procedures (catheters, pacemakers, prosthetic valves).
- The disease can be acute or subacute.

Predisposing Factors for Endocarditis

- Historically, Rheumatic Disease ...caused by Group A Streptococci was considered a frequent pre-disposing factor for endocarditis.

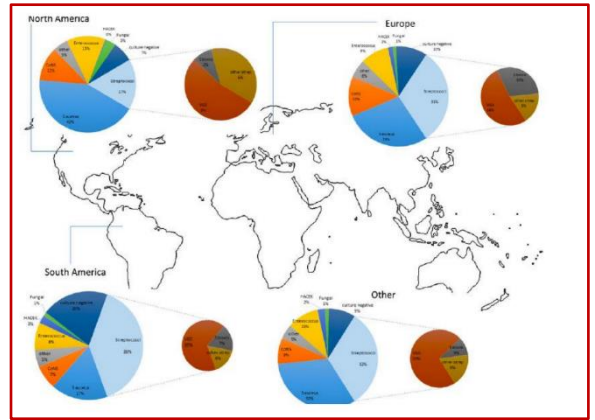
- Congenital heart disorders, Prosthetic heart valves Pacemaker, following pneumonia and meningitis.
- Periodontal procedures/disease, Damaged gingival tissue due to plaque accumulation on teeth.
- Dental extractions, Dental implants.
- Hemodialysis Tonsillectomy, Esophageal dilation.
- Skin infections... Intravenous drug users.
 - The tricuspid valve is the most affected valve in these people. **Staph aureus is the most common causative organism followed by coagulase negative staphylococci- staph epidermis.**
- Cystoscopy. Colonoscopy, Urethral dilation, TURP (transurethral resection of the prostate).
- All these procedures, associated with mucosal commensal flora, may cause endogenous infections. Thus Antibiotic Prophylaxis is recommended.
- We have what's called 'Native valve endocarditis' and 'Prosthetic valve endocarditis'.
 - Native -our normal – valve endocarditis is most often caused by streptococci (especially group A β -hemolytic which can be caused by a recurrent infection after rheumatic heart disease or viridans). However, prosthetic valve endocarditis is usually caused by staphylococci because staph is a skin commensal and an invasive procedure is required to access the circulation.

Microbiology Overview

- The microbiology of the disease has also changed, and staphylococci, most often associated with health-care contact and invasive procedures, have overtaken streptococci as the most common cause of the disease.
- The Gram-positive cocci of the staphylococcus, streptococcus, and enterococcus species account for 80–90% of infective endocarditis.

➤ streptococci and staphylococci have collectively accounted for approximately 80% of IE cases, the proportion of these two organisms varies by region

➤ The distribution of these gram-positive cocci differs world-wide; generally, in developing countries streptococci-group A beta hemolytic (can be caused by a recurrent infection after rheumatic heart disease) or viridans streptococci are the most common causative organisms and rheumatic heart disease is the common predisposing factor. **Viridans > strep group A**



➤ Staphylococci and most commonly *S aureus* is the most frequently isolated microorganism associated with infective endocarditis in high-income countries and is reported in up to 30% of cases.

➤ Streptococcal infective endocarditis caused by the oral viridans group (also can be found in the GI tract) remains most common in low-income countries. So, dentists give their patients antibiotics prophylactically in almost all procedures to avoid causing IE because these invasive procedures usually give access to the blood causing bacteremia.

➤ Enterococci (a gram-positive bacteria) account for 10% of cases overall (they come after staph and strep).

➤ Then, we have the fastidious bacteria including brucella (common in our region), tropheryma whipplei, bartonella, and Coxiella burnetii (cause of Q fever).

➤ These fastidious bacteria can't be cultured, we diagnose them by serology.

➤ The HACEK bacteria (Haemophilus, Aggregatibacter, Cardiobacterium, Eikenella corrodens, kingella), which cause about 3% of cases (very rare).

➤ Fungal endocarditis, usually Candida or Aspergillus or Histoplasma, is rare but often fatal, arising in patients who are immunosuppressed or after cardiac surgery, mostly on prosthetic valves.

➤ To remember the patients who might develop fungal endocarditis, always imagine a patient who is in the ICU taking broad- spectrum antibiotics and

is put on IV nutrition while being prepared for the insertion of a central catheter.

➤ Ponder the table well:

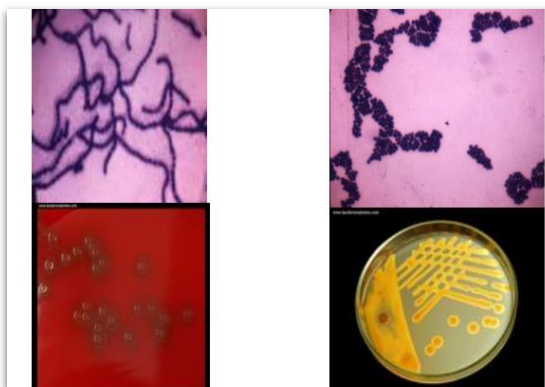
	Catalase	Coagulase	Hemolysis†	Distinguishing Features	Disease Presentations
<i>Staphylococcus</i> Species					
<i>S. aureus</i>	+	+	β	Ferments mannitol Salt tolerant	Infective endocarditis (acute) Abscesses Toxic shock syndrome Gastroenteritis Suppurative lesions, pyoderma, impetigo Osteomyelitis
<i>S. epidermidis</i>	+	-	γ	Novobiocin ^S Biofilm producer	Endocarditis in IV drug users Catheter and prosthetic device infections
Viridans group (not groupable)	-	-	α	Optochin ^R	Infective endocarditis Dental caries
<i>Enterococcus</i> sp. (Group D)	-	-	α, β, or γ	PYR [†] Esculin agar	Infective endocarditis Urinary and biliary infections
<i>S. bovis</i>	-	-	γ	Bile esculin [†]	Endocarditis, especially in patients with colon cancer

- For staphs: aureus is coagulase +, whereas epidermidis, Lugdunensis and capitis are coagulase -.
- One of the criteria used to classify streptococci is their pattern of hemolysis.
- Viridians (mainly mitis and mutans) are not groupable by Lancefield classification; they cause partial (alpha) hemolysis.
- Patients with colon cancer develop IE due to *S. Bovis* (non-enterococcus group D) mainly.

Microbial Causes -1

- Gram-positive cocci... facultative anaerobes, diplococci chains/clusters or pairs cocci... Catalase +ve /Staphylococci group.. catalase-ve/ Streptococci & Enterococci groups.
- Streptococci subdivided into groups according their hemolytic reaction on blood agar in vitro & by serotypes according to surface cell wall specific carbohydrate antigens.
- Viridans streptococci Group (VGS)
 - Normal oral-intestinal flora... Common causes of dental caries... Oral abscesses Gingivitis. Deposit dextran, adhesins, Fibronectin-binding protein (their virulence factor) which are needed to start the adhesion on the heart valves causing prerequisite 3, vegetation.

- *St. mutans*, *St. Mitis*, *St. Anginosus*, and *St. Salivarius* are accounted for many cases, and tend to be less susceptible to penicillins.
- They may get access to circulation causing the prerequisite number 1- Bacteremia.
- **Group A Streptococci (*S. Pyogenes* or strep throat) ... Repeated Sore throat infection... Less skin infection (impetigo)... Develop Post-streptococcal Diseases ..Rheumatic heart disease (carditis, joints, brain in the form of meningitis).. Children. Observed later in young adults (at 30).**
 - Might cause streptococcal glomerulonephritis.
 - Rheumatic heart disease and glomerulonephritis are called post infection syndrome which develop after a few weeks of infection because of molecular mimicry, caused by the mimicry between the M protein of the bacteria and other proteins in the cardiac muscle, brain and joints.
- *S. aureus* is a common cause of acute endocarditis in developed countries mainly, may result in a severe sepsis syndrome with a fatal outcome.
 - Most endocarditis cases occurred within 2-month-1 year following vascular catheters & surgical wounds, skin injury/ invasive dental procedures and others.
- Enterococcus species (*E. fecalis*, *E. faecium*) are responsible for up to 5-10% of cases; some strains may be resistant to penicillin, vancomycin.
 - Resistant Strains are usually treated with Teicoplanin.



Streptococci (forming strips) vs Staphylococci (forming clusters)

- Notice the partial hemolysis in streptococci on the blood agar.

- Staph aureus turns the mannitol salt agar medium (Differential and selective medium for staph aureus) extremely yellow.

Microbial Causes-2

- A group of fastidious gram-negative bacteria can cause rarely endocarditis: Gram-ve bacteria: Brucella, Salmonella, Haemophilus, Cardiobacterium, Eikenella, Gram+ve Actinobacillus part of Normal oral flora.
- Clinically, these bacteria spp. causing subacute or chronic course, and often present with embolic lesions from large biofilm vegetations in heart valves.

Yeast & Filamentous Fungi

- The most common species is Candida albicans, followed by other less common Candida spp. (C. glabrata, C. krusei, C. parapsilosis, C. tropicalis).
- Candida part of human normal flora.. Oral-intestinal-Urinary tract (Vagina).. Infection often followed often using catheters or respiratory intubation.
- Endocarditis due to Histoplasma capsulatum / Aspergillus species is very rare.. Immuno-suppressed patients (HIV, especially hospitalized ones) can also be infected.
- People who are in the ICU and receive prolonged Broad-spectrum antibiotic course with central line and peripherally inserted central catheters (central line: an intravenous catheter that is used to give medications, PICC: a Catheter that is used when parenteral nutrition is required, from google) might develop infective endocarditis due to fungal causes.

Candida albicans Pseudohyphae

In terms of morphology, candida are yeasts; however, they can claim other morphological forms which are pseudohyphae and true hyphae.



If they were grown on a special agar called **corn meal** agar, they would show pseudohyphae with chlamydospores formation under the microscope.

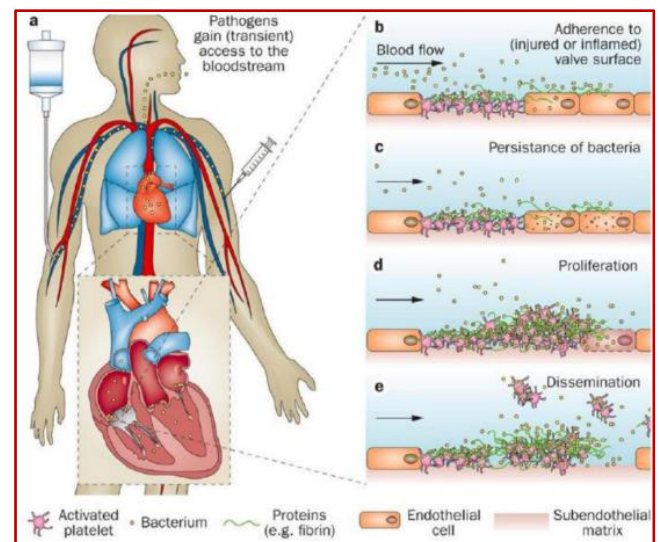


If they were grown on Sabouraud Dextrose Agar, they will form white, creamy, glabrous, waxy colonies.

Pathophysiology

- The healthy cardiac endothelium is resistant to frequent bacteraemia caused by daily activities such as chewing and tooth brushing.
- Bloodstream infection is a prerequisite for development.
- The development of IE requires the simultaneous occurrence of several independent factors:

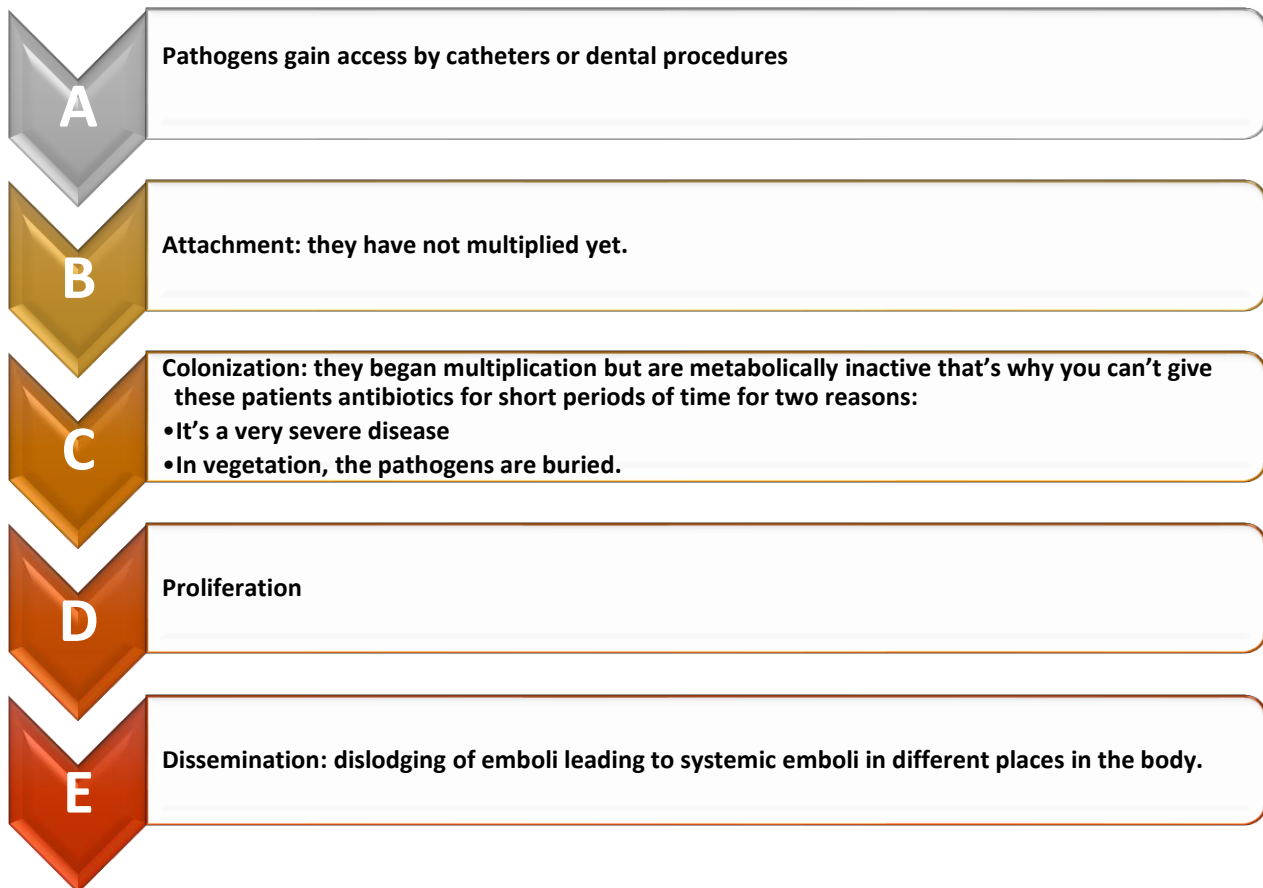
1. bacteraemia with an organism capable of attaching to and colonizing valve tissue;
2. alteration of the cardiac valve surface to produce a suitable site for bacterial attachment and colonization (by structural defect or inflammation of endothelial lining for native valves);



3. and creation of the infected mass or 'vegetation' by 'burying' of the proliferating organism within a protective matrix of serum molecules (for example, fibrin) and platelet A Biofilm .. Accumulation Bacteria, platelets, fibrin and few leucocytes.

- This mass can dislodge and cause emboli and infarction in very far places from the heart.

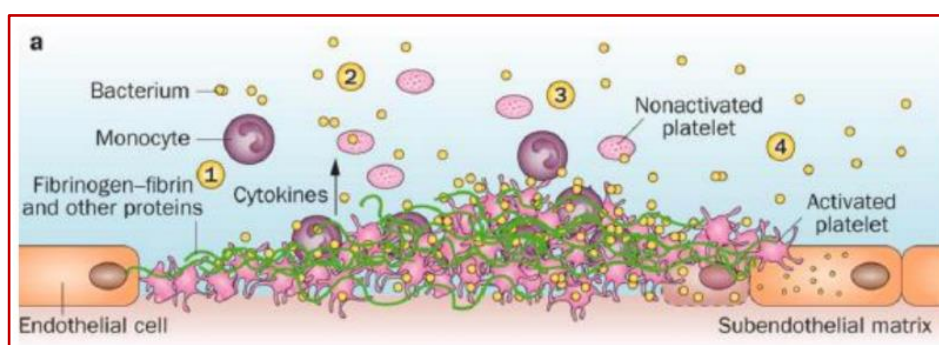
➤ Immuno-minor criteria.



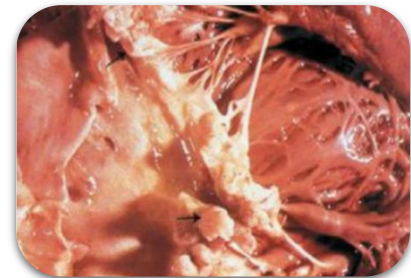
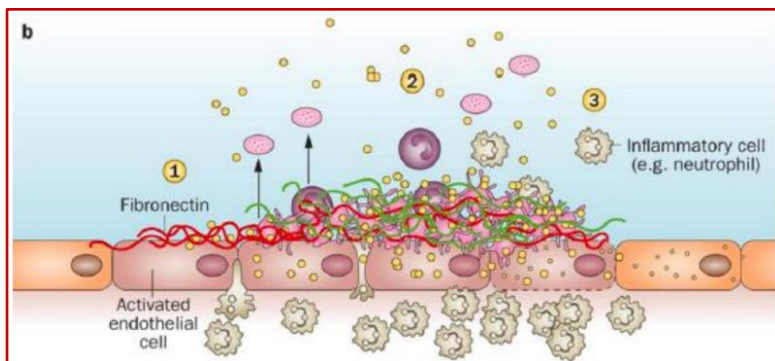
Does this mean that we should give antibiotics for any patient who has been through a dental procedure? It actually depends on the guidelines, incidence and prevalence, presence of risk factors, etc..., but in general, we give them prophylactically.

How does prerequisite two happen?

A- destruction to the endothelial lining → mechanical injury occurred which fulfils prerequisite two. Therefore, this will form a site that is available for attachment, colonization and proliferation for the bacteria present in blood. It can even cause internalization into the endothelial cells. As a result, we will get an immune response which will show us the immunological phenomenon. Keep in mind that the presentation can show vascular and immunological phenomena.



B- there is no mechanical injury to the endothelial lining but its inflamed. This can be native valve or prosthetic valve endocarditis. Most common involved valve is the mitral valve. However, if they were IV drug abusers, it would be the tricuspid valve.



This is a mitral valve. The arrow is pointing towards a vegetation which is prerequisite 3. It can dislodge completely or partially (seeding occurs).

Clinical features

- The clinical presentation of infective endocarditis is particularly diverse and **non-specific**. Most commonly fever (90- 95%), so IE should be considered as a differential diagnosis in any patient with fever of unknown origin. Secondly (80-85%), murmur whether of new onset or and old one that has changed.
- **Acute endocarditis is a hectically febrile illness that rapidly damages cardiac structures, seeds extracardiac sites, and, if untreated, progresses to death within weeks** (remember it is caused by staph. aureus, group A β -haemolytic streptococci and Strep. Pneumonia).
- **Subacute endocarditis follows an indolent course; causes structural cardiac damage only slowly (takes years), if at all; rarely metastasizes; and is gradually progressive unless complicated by a major embolic event or a ruptured mycotic aneurysm.** Fever won't be as high as in acute endocarditis as well as the developing complications of IE. (Caused by strep. Viridians, entero, strep.bovis, and the rest)
- A patient can come after dislodgment of the emboli with signs and symptoms related to the place of systemic emboli or infarction.

Cardiac Manifestations

- Although heart murmurs are usually indicative of the predisposing cardiac pathology rather than of endocarditis, valvular damage and ruptured chordae may result in new regurgitant murmurs.
- Congestive heart failure (CHF) (only presentation of a patient with IE) develops in 30–40% of patients as a consequence of valvular dysfunction.

Noncardiac Manifestations

- These manifestations depend on the site of the infarction that is caused by the dislodged emboli, which can be the lungs, the brain (causing stroke), the periphery, etc...
- The classic nonsuppurative peripheral manifestations of subacute endocarditis (e.g., Janeway lesions are related to prolonged infection, they appear as erythematous papules).
- In contrast, septic embolization mimicking some of these lesions (subungual hemorrhage, Osler's nodes) is common in patients with acute *S. aureus* endocarditis.



Janeway lesions



Janeway lesions



Osler's nodes

Janeway

- painless
- non-tender
- **vascular** phenomenon

Osler

- painful
- emboli related
- **immunological** phenomenon

- **Roth spots** (in the eye) are part of the immunological phenomenon like osler nodes.
- **Conjunctival hemorrhage** is part of the vascular phenomena like Janeway lesions.

DIAGNOSIS

- The diagnosis of IE typically requires a combination of clinical, microbiological and echocardiography results (not easy).
- Blood culture is the most important initial laboratory test in the workup of IE. Bacteraemia is usually continuous and the majority of patients with IE have positive blood cultures.
- Echocardiography is the second cornerstone of diagnostic efforts and should be performed in all patients in whom IE is suspected.
- A highly sensitive and specific diagnostic schema—known as the modified Duke criteria—is based on clinical, laboratory, and echocardiographic findings commonly encountered in patients with endocarditis.
 - It categorizes patients based on risk factors as definite, possible or reject using major and minor criteria.
 - Definite: 2 major criteria or 1 major & 3 minor
 - Major criteria are basically:
 - 1- microbiological evidence (blood samples taken at different times all giving a positive result for a causative agent).
 - 2- Echocardiography: transoesophageal or transtracheal → showing structural defect in heart. In case of the presence of prosthetic valves, there will be partial dehiscence. Sometimes, we can even see vegetation.
 - Minor criteria: fever, patient has predisposition factors, the patient is an IV drug abuser, patient has vascular or immunological phenomena.
- **Non-Blood-Culture Tests (for the HACEK group (because they give culture negative results)):** Serologic tests culture, microscopic examination with special stains, (i.e., the periodic acid–Schiff stain for *T. whipplei*), direct fluorescence antibody techniques and by the use of polymerase chain reaction to recover unique microbial DNA or DNA encoding the 16S or 28S ribosomal unit.
- Echocardiography

Management

➤ ANTIMICROBIAL THERAPY

- Vancomycin plus Gentamicin initiated immediately after blood samples are taken for cultures.
 - Doesn't work for enterococci.
 - We give 3rd generation cephalosporin (or ceftriaxone, which is a 3rd generation cephalosporin) for gram negative bacteria.
 - vancomycin is given by IV administration (used orally only for treating difficile – associated diarrhea).
 - These drugs are used for a long period of time.
- Extended courses of parenteral therapy with bactericidal (or fungicidal) agents are typically required.
 - Antifungal agents like amphotericin b for fungal infections (antibiotics won't be beneficial in this case).

➤ Surgical Treatment by a cardiothoracic surgeon.

- to decrease prerequisite 2 (structural defect in heart which gives a suitable environment for attachment and colonization of bacteria).

PREVENTION

- To prevent endocarditis (long a goal in clinical practice), past expert committees have supported systemic antibiotic administration prior to many bacteraemia-inducing procedures.
 - Invasive procedures and other risk factors → Prophylactic antibiotics (just to be on the safe side).

Good luck

"اللهم اجعل ثأرنا على من ظلمنا وانصرنا على من عادانا... اللهم إن كان هذا أو أن استبدال، فاستعملنا ولا تستبدلنا.. إنا إليك راغبون".

V5

- Page 9: It was CHROMagar in V1; CHROMagar is used to distinguish between candida species. The right medium is corn meal.
- Text highlighted in red.
- V5:
 1. page 3 (prerequisites)
 2. page 12 (roth spots and conjunctival hemorrhage)

We apologize for the various versions that have been uploaded; there were many deviations in the information between the lectures. ♥