Infective Endocarditis

Objectives:

- Understand the definition of Endocarditis.
- Know the pathophysiology of endocarditis.
- Know the risk factors for endocarditis.
- Know the presentation of patients with endocarditis.
- How to diagnose endocarditis.
- Know the treatment of endocarditis.
- Know the complications of endocarditis.
- Know the ways to prevent endocarditis.

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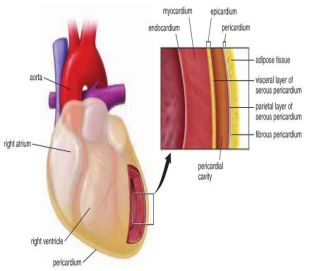
Introduction to Infective Endocarditis (IE)

- **Review:** The heart wall is composed of three layers which includes:
  1. **Innermost layer:** endocardium: it is part of muscle and endothelial tissue (Inflammation = Endocarditis)
  2. **Middle layer:** myocardium : it is muscle (Inflammation = Myocarditis)
  3. **External layer:** epicardium :it is thick membrane covers the heart from outside (Inflammation = Pericarditis)



Pancarditis : inflammation of all layers of the heart.

Inflammatory process whether it is infective or noninfective can affect any layer of the heart.

Definition:

Infective endocarditis is an infection of the endothelial surface of the heart which includes:

1. Heart valves (valvular apparatus including chordae tendineae and papillary muscle)
2. Septal defects[1]
   a. Interatrial septum defect : which can create a shunt
   b. Interventricular septum defects
3. Chordae Tendineae
4. Arteriovenous shunt[2] .

Infective endocarditis can affect : 1- valvular apparatus/ 2- endocardium inside wherever there is congenital or structural abnormality/ 3- additional structure like prostheses ; for example if patient has VSD closed with dacron artificial patch (not animal patch) , this patch becomes part of endocardium and can be part of endocarditis as well.

Pathophysiology and Risk Factors of IE

- **Pathogenesis:** Infective endocarditis is the net result of the complex interaction between multiple factors 1- the bloodstream pathogen 2- matrix molecules (fibrin and thrombin) interact with platelets at sites of endocardial cells damage forming VEGETATION which is the hallmark of endocarditis.

[1] 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).

[2] 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.

1. Endothelial Damage	• Caused by turbulent blood flow produced by either a congenital or acquired heart disease. This flow can be from a high to a low pressure chamber, high velocity jet, or across a narrowed orifice which traumatizes the endothelium. • Valves transfer blood from one chamber to another so when the heart contracts it will push the blood through aortic and pulmonary valve . If one of them is stenotic , then the contraction against narrowed valve creates very high pressure and this will create very high turbulence . The turbulence itself might injure the endothelium. • Similarly if there is a interventricular septal defect the blood flow from high pressure chamber L.T ventricle (120) to low pressure chamber R.T ventricle (10) causes turbulence resulting in endothelial injury.Pressure difference : 120-10 =110 , pressure difference is huge so the likelihood of development of endothelial damage is more ! • Another example, Mitral regurgitation . The valve is not closing well, so instead of blood going to aorta during systole it will go to L.T atrium through mitral valve and that creates turbulence and endothelial injury. • The higher difference between two chambers the more turbulent blood flow becomes.Thats' why ASD is less likely to develop IE. Maximum R.T atrium pressure 10, L.T atrium pressure 15 , pressure difference : 15-10 =5 . **Who is susceptible for endothelial damage ?** 1- people with valve disease/ 2- people with prostheses/ 3- people with congenital anomaly
2. Formation of Non-Bacterial Thrombotic Endocarditis (NBTE)	• Endothelial damage creates a predisposition for deposition of platelets and fibrin on the surface of the endothelium, which results in NBTE. • The endothelial surface becomes rough and it will recruit inflammatory cells (WBC and platelets) towards it . Inflammatory and immunological reaction for damage forms platelet thrombin and fibrin plug which we called NBTE.
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. This will releases many different microbial species transiently into the bloodstream which will leads to Transient bacteremia caused by organisms e.g. Viridans group streptococci. • Bacteria live inside human body as commensal, oral cavity GI and genitalia are the sources of heavily populated bacteria.
4. Transient Bacteremia:	• Invasion of the bloodstream with a microbial species that has the pathogenic potential to colonize this site (endocardium)
5. Bacterial Adherence:	• This will result in the proliferation of bacteria within NBTE forming vegetation the hallmark of Infective Endocarditis. **NBTE + Microorganism (bacteria) = Vegetation = IE**

In doctor's slides, (steps 3,4 and 5) are fused in 1 step. It is the same concept but different way of presentation.

Risk Factors:

The risk is determined based on:

- The presence or absence of a cardiac condition (as mentioned down : 1b,1c,1d,1e, 2a)
- The type of procedure to be done (mainly dental) (as mentioned down : 1a, 2b,2c,2d,2e,2f)

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

1. **High risk:** (Needs Prophylaxis)

   Risk of bacteremia in Dental procedures that involve manipulation of gingival tissue, peri-apical region of teeth, or perforation of the oral mucosa in patients with the following:

   a. Prosthetic valves (400x risk , Highest risk)
      - Prosthetic cardiac valves, including trans-catheter-implanted prostheses & homografts.
      - Prosthetic material used for cardiac valve repair, such as annuloplasty rings & chords.

   b. History of previous endocarditis.

   c. Congenital heart defect such as Complex cyanotic disease (Tetralogy, Transposition, Single Ventricle), Patent Ductus Arteriosus, VSD and Coarctation of aorta.
      - 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.

   d. Cardiac transplant with valve regurgitation due to a structurally abnormal valve.
      For patient with cardiac transplant it is really dangerous to have endocarditis it will damage the heart and may lead to death.

To sum up : According to guidelines prophylaxis is given only for patient with the risk factors mentioned above when they undergo some dental procedures that will cause damage to mucosal surface.

2. **Low risk:** (Does NOT need Prophylaxis)
   - 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.

Classification of Infective Endocarditis

Infective Endocarditis is classified according to:

1. **The nature of the valve involved:**
   a. Native valve (congenital heart disease)
   b. Prosthetic valve (more dangerous and the treatment is radical you have to go and remove the valve)
2. **Onset and progression:**
   a. **Acute:** within 24 Hrs
   - Most commonly by Staph. Aureus
   - Occurs in a normal heart valve
   - If untreated, fatal in less than 6 weeks

   b. **Sub-acute:** takes longer time to develop 4 to 6 weeks after dental procedure
   - Causes by less virulent organisms, ex: Streptococcus viridans and Enterococcus
   - Occurs on damaged heart valves
   - If untreated, Takes much longer than 6 weeks to cause death
3. **Acquisition of the infection:**
   a. Nosocomial (hospital acquired) for example: IE caused by recent prosthetic valve replacement
   b. Community.

- **Causative Organisms of IE:** Why do we suspect the organism? For immediate treatment

Native Valve Endocarditis	IV-Drug Abusers	Prosthetic Valve Endocarditis Might come in exam
1. **Streptococci Viridans** (The commonest organism) 2. Staphylococci (25%): Mostly Coagulase +ve Staph. Aureus Or Staph. Epidermidis 3. Enterococci (~10%) **4.** HACEK: (Treatment: ceftriaxone) • Haemophilus	• Skin most predominant source of infection • 70 - 100% of Right sided IE results in pneumonia and septic emboli 1. Staph aureus (because it's on the skin) 60% 2. Streptococci and Enterococci 20%	A. **Early onset:** • within 60 days after surgery • Reflects perioperative contamination • Incidence around 1% • Microbiology: 1. Staph (45-50%) •Staph. Epidermidis (~30%)

• Actinobacillus • Actinomycetemcomitans • Cardiobacterium hominis • Eikenella • Kingella	3. Gram -ve bacilli 10% 4. Fungi (Candida and Aspergillus) 5% (the only situation that normal person can have infective endocarditis without cardiac problem is in IV drug abuse)	•Staph. Aureus (~20%) 2. Gram -ve aerobes (~20%) 3. Fungi (~10%) 4. Strep and Entero (5-10%) Prosthetic valve endocarditis like drug abusers caused by Staph.aureus only when developed within 60 days after surgery 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 viridans**

The doctor said that Streptococci Viridans and Staph aureus are important.

The Clinical Features & The Investigations of IE

- **Clinical Features:**

The onset is usually within 2 weeks of the infection:

1. **indolent course** would include: subacute
   fever, malaise, fatigue, night sweats, anorexia and weight loss.

2. **explosive course** would include: pt comes with complications
   Congestive cardiac failure (CCF), new or changing murmur with severe systemic sepsis. new onset or changing character murmur.

3. **Other features, include :**

Immunological Manifestations	Vascular & Septic Emboli	Others
1. Osler Nodes[3] (10-25%): Painful nodules 2. Roth Spots[4] ~5% : red spots like vasculitis inside retina. 3. Glomerulonephritis. 4. +ve Rheumatoid Factor. Immunological features happened when there is antigen-antibody reaction away from heart.(kidneys: glomerulonephritis) , (in retina : roth spots), (in joints: +ve RF), (in skin: Osler's nodes).	1. Splinter hemorrhage (5-10%) 2. Janeway Lesion[5] 3. Subconjunctival Hemorrhage 4. Mycotic Aneurysm 5. Arthritis 6. Hematuria Septic emboli can cause vascular necrosis of distal part of finger leading to gangrene but in very limited situations	1. Splenomegaly (30%) Petechiae[6] (20-40%) • conjunctival • buccal mucosa • palate hemorrhage • skin in supraclavicular area **(Petechiae is vascular manifestations)**

You have to differentiate between immunological features and features caused by vascular and septic embolism.

➢ Mnemonic for the signs & symptoms of IE is FROM JANE

Q : Why do they have anaemia ?
1- Anaemia of Chronic illness.
2- Hematuria secondary to septic embolization to glomeruli.
3- Haemolytic process secondary to underlying immunological mechanism.
It is multisystemic disease can affect any part of your body.

• Investigation:

- C.B.C (looking for anaemia or leukocytosis)
- ESR (increases with chronic illness)
- Blood cultures (to identify the microorganism)
- Renal Function Test
- Urinalysis (looking for hematuria)
- ECG (for any conduction abnormality as a result of local destruction it may cause arrhythmia)
- Chest X-ray (pneumothorax or hemothorax, rarely)
- Echocardiogram (TEE) (to see the vegetation)

[3] Painful, red, raised lesions found on the hands and feet
[4] Retinal hemorrhages with white or pale centers
[5] painless erythematous skin lesions in the palm and sole.
[6] A **petechia** is a small (1–2 mm) red or purple spot on the skin, caused by a minor bleed from broken capillary blood vessels

Diagnostic Criteria of IE (Duke Criteria)

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

Diagnosis of IE:

(The next slide will tell you how many major / minor features are required to diagnose Infective Endocarditis)

Major Criteria

1-Blood Culture positive for IE:

A- 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

B- Microorganisms consistent with IE from persistently positive blood cultures:

≥2 positive blood cultures of blood samples drawn >12 hrs apart; or

C- single positive culture for coxiella burnetii or phase I IgG antibody titre > 1:800

2-Imaging positive for IE:

A- Echocardiogram positive for IE:

- Vegetation : echo shows us the size and extension of vegetations
- Abscess , pseudoaneurysm ,intracardiac fistula
- Valvular perforation or aneurysm
- New partial dehiscence of prosthetic valve

B- 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 radiolabeled leukocytes SPECT/CT.

C- Definite paravalvular lesion by cardiac CT.

Minor Criteria

1.Fever : defined as temperature >38C.

2.Echo Finding: (Any finding not involved in the major criteria) (calcifications for example)

3-Vascular Phenomena (including these detected only by imaging):

major arterial emboli , septic pulmonary infarcts , infectious (mycotic) aneurysm , intracranial hemorrhage , conjunctival hemorrhage and janeway's lesions.

4.Evidence from Microbiology : positive blood culture but does not meet a major criterion as noted above (in major criteria 1) or serological evidence of active infection with organism consistent with IE.

5.Risk factors and Predisposition: such as heart condition or injection drug user.

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

- Blood culture and imaging +ve for IE are the most likely investigations that provide definitive diagnosis of IE.

1. Definitive infective endocarditis:

- **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.
- **Clinical criteria:**
  Based on DUKE criteria 2015 by either:
  2 major criteria , 1 major + 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 + 1 minor or 3 minor
- Based on the physician's experience, he/she will decide to diagnose and treat or not.

3. Rejected infective endocarditis: **(like for example patient have the all manifestation but it is because other disease) (does not consider as IE)**

- Firm alternate Diagnosis 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

❖ **SLE disease can cause Libman sacks endocarditis (non-infective endocarditis)**

Management of Infective Endocarditis

• Treatment :

1-Medical (Antibiotic):

Principles of Medical Management: treat vegetations with antibiotics **prolonged , high dose and bactericidal.**

❖ **Acute onset:** blood culture and start treatment within three hours with your clinical suspicion of organism

❖ **Sub-acute onset :** Blood culture then antibiotic can be started within three days.

A-Penicillin susceptible streptococcus viridans or bovis :

- Once daily ceftriaxone (third generation cephalosporin) (or i.v. penicillin G or i.v. amoxicillin) for 4 weeks ;or
- Ceftriaxone 2g for 2 weeks followed by oral amoxicillin for 2 weeks.

- (In b-lactam allergic patients: Vancomycin)

Prosthetic valve may need longer treatment durations.

B-Methicillin susceptible Staphylococcus :

- Flucloxacillin ,
- (In b-lactam allergic patients: Vancomycin).

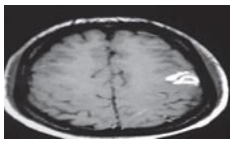
  - ❖ Empirical treatment depends on the mode of presentation,the suspected organism, and whether the patient has a prosthetic valve or penicillin allergy.
  - ❖ If the presentation is acute, flucloxacillin and gentamicin are recommended, while for a subacute or indolent presentation, benzyl penicillin and gentamicin are preferred.

2-Surgical: whenever indicated for example in prosthetic valve infective endocarditis

Indications for surgery : 1-Prosthetic valve endocarditis 2-large Vegetation 3-Embolization (recurrent while on antibiotics) 4-heart failure due to valve damage 5-Fungal Endocarditis 6-Abscess

Complications of IE

This vegetation can cause local destruction or distant embolisation

Congestive Cardiac Failure: (Most common)	**Neurological Manifestations: ⅓ of cases**
• Valve Destruction • Myocarditis • Coronary artery embolism and MI • Myocardial Abscesses	• Major embolism to MCA territory ~25% • Mycotic Aneurysms 2-10% in brain can cause hemorrhage 
Metastatic infections	**Renal impairment (Glomerulonephritis)**
• Rt. Sided vegetations: Lung abscesses Pyothorax / Pyo-pneumothorax[7] • Lt. Sided vegetations: Pyogenic Meningitis Splenic Abscesses Pyelonephritis Osteomyelitis Renal impairment and glomerulonephritis	As a result of immunological phenomena.

[7] **Pyopneumothorax** (also known as infected hydropneumothorax or empyemic hydropneumothorax) is a pleural collection of pus and air.

Prophylaxis and Prevention

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

For dental procedure at risk :(only in these situation we use prophylaxis)
Amoxicillin or Ampicillin 2 g orally 1-2 hours before the procedure.
(If Allergic to penicillin or ampicillin: Clindamycin 600 mg)

- **Main principles of prevention in IE: (if patient has cardiac disease problem and he will undergo procedure that could expose to bacteremia like tooth extraction we give antibiotic)**

  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 is the incidence of IE needs further investigations.
  6- avoid unnecessary use of antibiotic to reduce the resistance

Summary

- Infective endocarditis (IE) is an infection involving the endocardial surface of the heart, including the valvular structures, the chordae tendineae, sites of septal defects, or the mural endocardium.
- Presentation is often nonspecific and most commonly includes fever.
- Historical sources of bacteremia should be considered, such as indwelling vascular catheters, recent dental work, and intravenous drug use.
- Symptoms are often subtle and exam is often unrevealing, but may demonstrate cardiac murmur, peripheral emboli, Osler nodes, Roth spots, and Janeway lesions.
- Three sets of blood cultures should be obtained prior to initiation of antibiotic therapy.
- An echocardiogram should be obtained in all suspected cases.
- Treatment is guided by presentation, clinical findings, and organism virulence.

Clinical Features **FROM JANE**	F- FEVER R- ROTH SPOT O- OSLER NODE M- MURMUR J- JEANWAY LESION A- ANEMIA N- NAIL HG (SPLINTER HG) E- EMBOLI Osler nodes, Roth spot, Gomeriolo-nephritis, Rheumatoid factor + are immunological reactions
Risk factors	• prior hx of infectious endocarditis • presence of artificial prosthetic heart valves • certain types of congenital heart disease • post heart transplant (patients who develop a cardiac valvulopathy)
Investigations	➔ C.B.C looking for anaemia ➔ ESR increases with chronic illness ➔ Blood cultures to identify the microorganism ➔ Renal Function Test ➔ Urinalysis looking for hematuria ➔ ECG for any conduction abnormality as a result of local destruction it may cause ➔ Chest X-ray (pneumothorax or hemothorax, rarely) ➔ Echocardiogram to see the vegetation

Examine Yourself !!

1. Mitral valve prolapse complication A 25-year-old woman with known mitral valve prolapse develops a low grade fever, malaise and night sweats within a couple of weeks of a major dental procedure. Examination reveals a pulse rate of 110/minute, which is regular, tender vasculitic lesions on the finger pulps and microscopic haematuria. Which investigation is most likely to provide a definitive diagnosis?

A.Full blood count B.ECG C.Autoantibody screen D.Blood culture E. Coronary angiography

2. Mitral valve prolapse An asymptomatic 31-year-old woman has been referred for cardiological assessment. After her ECG she was told that she had mitral valve prolapse and would like further information on this condition. Which of the following statements is correct?

A. Beta-blocker therapy is indicated.
B. Angiotensin-converting enzyme (ACE) inhibitor therapy is indicated
C. One or both leaflets of the mitral valve are pushed back into the left atrium during systole
D. Significant mitral regurgitation will eventually develop
E. Exercise should be restricted.

3- A 27 years old female patient presented with fever. Before 4 weeks she underwent a dental procedure. 2 years ago her mitral valve was replaced by prosthetic valve. The ER physician suspect that she develop endocarditis. what is the empirical antibiotic in her case?

A. a. Ceftriaxone.
B. Erythromycin.
C. Cefixime.
D. Gentamycin.

4- What are the procedure that associated with developing endocarditis in cardiac patients?

A. Laryngoscope.
B. upper GIT endoscopy.
C. gingival manipulation.
D. transurethral prostatic procedure.

5- Which of the following is a minor criterion of endocarditis?

A) Prolonged PR interval
B) -ve blood culture.
C) Osler's Nodules.
D) +ve blood culture.

6- A 20-year-old male presented to the ER with two weeks history of fever and malaise. Physical examination revealed a new onset diastolic murmur in the mitral area radiating to the axilla. Which of the following is expected to be found in the eye of this patient?

A- Janeway lesion
B- Osler's node
C- Roth's spot
D- splinter hemorrhage.

7- Patient underwent plastic surgery, within 18 hours of the surgery, she developed fever and murmurs. Her physician suspect endocarditis and he want to start the treatment immediately. Which one of the following is the best drug?

a. Ceftriaxone
b. Erythromycin
c. Flucloxacillin
d. 2nd generation of cephalosporin.

8. A 55 -year-old man with mitral stenosis is evaluated with new onset of fever, malaise. he noticed painful lesions on the fingers. His examination is significant for multiple painful red spots on the fingertips, a diastolic murmur and a pansystolic murmur. Which of the following is the likely diagnosis?

A. Atrial myxoma
B. Infective endocarditis
C. Rheumatic fever
D. Ruptured mitral valve

9- Doctor: I will ask about Duke criteria in diagnosing infective endocarditis.

These are the clinical criteria described at Duke University, North Carolina, for the diagnosis of infective endocarditis (see K&C 7e, p. 769). The two major criteria are a positive blood culture and evidence of valvular disease, either clinical or echocardiographic. Minor criteria include fever, evidence of emboli, etc. Two major or one major and three minor are required for the diagnosis of infective endocarditis.

10- Doctor : Is Staphylococcus aureus the most frequent causative agent of acute bacterial endocarditis? And is this typical of acute bacterial endocarditis?

Staph. aureus is the most common cause of acute bacterial endocarditis. The clinical picture is very typical.

11- Please explain the mechanism of the mycotic aneurysm in IE.

Small septic emboli block vasa vasorum or a small distal cerebral artery itself, leading to damage to the muscular layer with dilatation and aneurysm formation.

12-Why are the right valves more commonly affected in infective endocarditis, when the microbes enter through the IV route, for example with IV drug users?

Because a large number of organisms go directly to the valves on the right side. However, even in intravenous drug users, left-sided valve involvement is more common.

13- What causes splenomegaly in infective endocarditis?

This is probably due to chronic infection with stimulation of both humoral and cellular immunity.

14- We know that Janeway lesions appear with infective endocarditis, but is there any other disease that can cause it?

Janeway lesions are fairly specific for infective endocarditis.

Answers

Q1 . The diagnosis here is subacute bacterial endocarditis, probably due to Streptococcus viridans. The definitive diagnosis is by blood culture (D) although echocardiography (B) will show vegetations on affected heart valves. Although the lesions described are vasculitic (as are the painless Janeway lesions and the Roth spots in the retina), in this case they are due to antigen–antibody complexes triggered by infection.

Q2. There is no indication for ACE inhibitor therapy (B), while beta-blockers (A) may be used for management of arrhythmias if these occur. Mitral regurgitation (D) is unlikely to occur, although it is a possibility. There is no need to limit exercise (E) in an asymptomatic patient.

3- D / 4- C / 5- C / 6- C / 7- C / 8- B