Cardiovascular System Infections

Learning objectives

- At the end of this session, students will be able to understand:

➢ Infective Endocarditis

➢ Other Infections of CVS

➢ Acute Rheumatic Fever

Introduction

- Cardiovascular system infections- infections of heart & blood vessels
- ➢ Infections of heart: infection of 3 layers of heart- endocardium, myocardium, pericardium
- ➢ Infections of blood vessels
- ➢ Device-related infections
- ➢ Autoimmune-mediated

Introduction

Cardiovascular System	Infections
Endocardium	Infective endocarditis
Myocardium	Myocarditis
Pericardium	Pericarditis, Pericardial effusion
Blood vessels	Mycotic aneurysm, Infective endocarditis
Device related	Catheter-related blood stream infection (CRBSI)
Autoimmune mediated	Acute Rheumatic Fever

Infective Endocarditis (IE)

- Microbial invasion of heart valves or mural endocardium
- Formation of bulky friable *vegetations*- composed of mass of platelets, fibrin, microcolonies of organisms, scanty inflammatory cells
- Site of *vegetations*: heart valves, low-pressure side of ventricular septal defect (VSD) & mural endocardium
- Classification: acute & subacute- based on rapidity of evolution, severity of infection & virulence of organism

Acute & Subacute Endocarditis

Acute endocarditis	Subacute endocarditis
Evolution- rapid	Evolution- slow
Involves normal cardiac valve	Involves previously damaged heart (scarred or deformed valve)
Implicated organism- high virulence e.g. *S. aureus*	Implicated organism- low virulence e.g. viridans streptococci
Causes substantial morbidity & mortality even with appropriate antibiotic therapy &/or surgery	Follows gradually progressive course of weeks to months; patients recover after antibiotic therapy
Less common type Accounts for 10-20% of all cases	More common type Accounts for 50-60% of all cases

Pathogenesis of Infective Endocarditis

- **Underlying risk factors**:
  - Underlying cardiac defect (mitral regurgitation, aortic stenosis & regurgitation, VSD)
  - Use of intravenous catheter
  - Prosthetic valve replacement surgery
- **Endothelial injury:**
  - Infective endocarditis- on injured valves
  - Predisposing abnormality, IV catheter→ damage endothelium→ deposition of platelets & fibrin→ thrombus formation- Non-bacterial thrombotic endocarditis (NBTE)

Pathogenesis of Infective Endocarditis

- **Colonization:**

➢ Thrombus- site for bacterial attachment

➢ During transient bacteraemia, organisms adhere to thrombus→ colonize & damage endothelial surface

- **Formation of vegetation:**

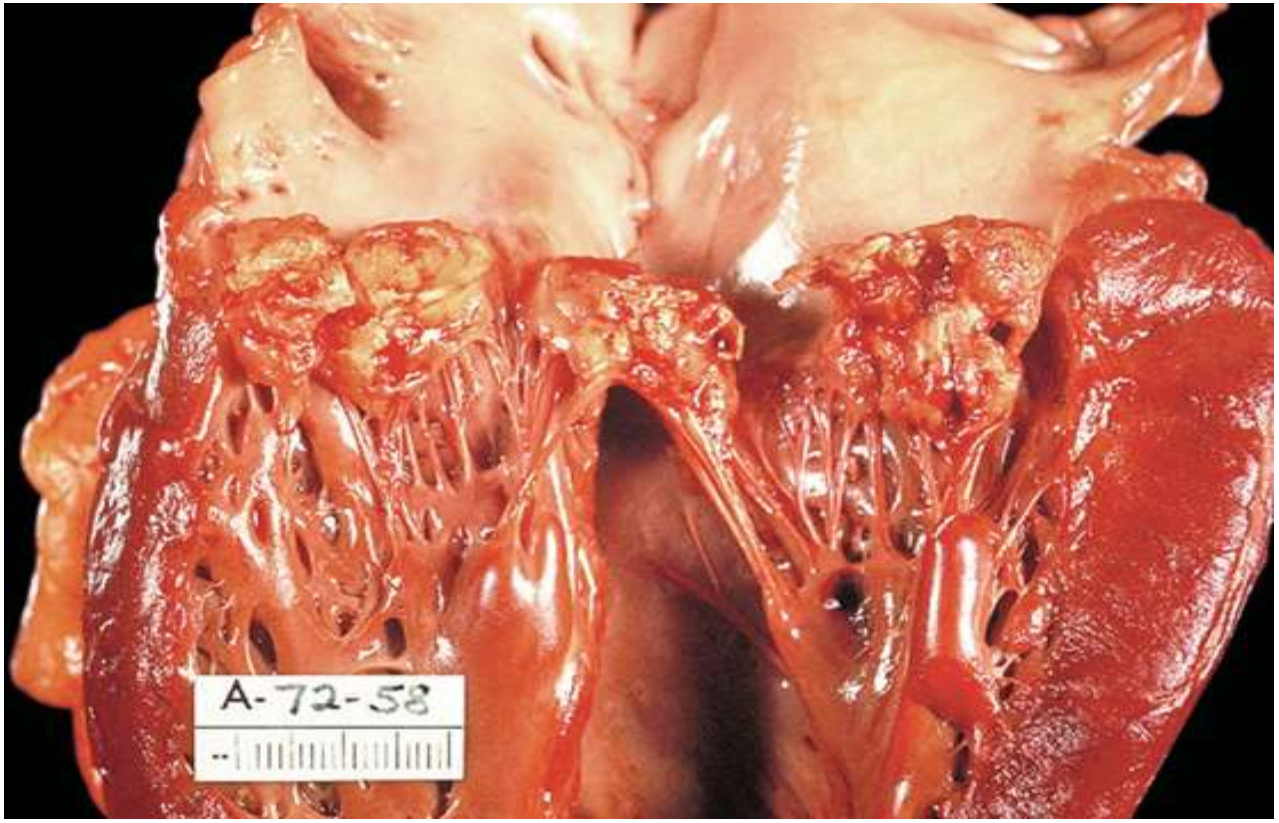
➢ After colonization: endothelial surface gets covered with fibrin & platelets→ further bacterial multiplication

➢ Platelet+ fibrin+ inflammatory cells: surround entrapped organisms→ produce *vegetation*

- **Metastasis:**

➢ Vegetation: seed bacteria into blood stream at slow & constant rate→ metastasis at distant sites

Pathogenesis of Infective Endocarditis



Subacute bacterial endocarditis involving mitral valve showing large *vegetations* on valve leaflets

Etiological Agents of IE

- Causative agents of IE differ depending on
- ➢ Underlying risk factors- native or prosthetic valve IE
- ➢ Acute or subacute IE
- ➢ IV drug abuser

Etiological Agents of IE

- *Staphylococcus aureus*
- Coagulase-negative staphylococci (*S.epidermidis*)
- *Streptococci* (Viridans streptococci & others)
- *Enterococci*
- *Pneumococci*
- Fastidious gram-negative coccobacilli (HACEK group)
- Enterobacteriaceae
- *Pseudomonas* spp. (in drug users)
- *Candida* species
- Diphtheroids

Etiological Agents of IE

Most common agent in specific types of endocarditis

Native valve endocarditis: *Staphylococcus aureus*

- Community acquired- Viridans streptococci
- Healthcare associated- *S. aureus*
- Overall- *S. aureus*

Prosthetic valve endocarditis: following cardiac valve replacement

- **Early** prosthetic valve endocarditis (within 12 months)- nosocomial, results from intra-operative contamination of prosthesis or bacteremic postoperative complication e.g. CoNS (*S.epidermidis*), *S. aureus*
- **Late** prosthetic valve endocarditis (after 12 months)- community-acquired- viridans streptococci
- **Overall:** regardless of time of onset after surgery- CoNS- majority Methicillin resistant

Etiological Agents of IE

- **Endocarditis in IV drug abusers**: young males- common victims (skin- commonest source)

➢ **Right-sided (tricuspid valve) endocarditis**- *S. aureus* majority MRSA

➢ **Left-sided (mitral valve) endocarditis**- varied etiology *Enterococcus*, *S. aureus*. *Pseudomonas aeruginosa*, *Candida* species & sporadically unusual organisms- *Bacillus*, *Lactobacillus*, *Corynebacterium* spps.

➢ **Overall**: *Staphylococcus aureus*

➢ Subacute endocarditis: Viridians streptococci

Etiological Agents of IE

- **Culture-negative endocarditis**: 5-10% of IE- negative blood cultures; majority (one-third to one-half) because of prior antibiotic exposure. Remainder patients infected by fastidious organisms:

➢ Nutritionally variant streptococci (Granulicatella, Abiotrophia)

➢ HACEK organisms

➢ *Others- Coxiella burnetii, Bartonella* species, *Brucella* species, *Tropheryma whipplei* (causes indolent, culture-negative, afebrile form of endocarditis)

➢ Some fastidious organisms occur in characteristic geographic settings (*C.burnetii, Bartonella* species in Europe, *Brucella* species in Middle East)

Clinical Manifestations

- **Cardiac manifestations**:

➢ Appearance of new/worsened regurgitant murmur- useful for diagnosis of IE involving normal valve

- **Non-cardiac manifestations**:

➢ Fever, chills & sweats, anorexia, weight loss, myalgia, arthralgia, arterial emboli, splenomegaly, clubbing, petechiae, neurologic manifestations and peripheral manifestations (Osler's nodes, Janeway lesions, subungual haemorrhages)

- **Laboratory manifestations**:

➢ Anaemia, leucocytosis, microscopic haematuria, elevated ESR, CRP, or rheumatoid factor

Diagnosis (Modified Duke Criteria)

Major Criteria

1. Positive blood culture: any one of the following:

A. Typical IE organism isolated from two separate blood culture sets (Viridans streptococci, *Streptococcus gallolyticus*, HACEK group, *S. aureus,* enterococci) OR

B. Persistently positive blood culture with agents other than typical IE organisms:

- 2 Blood culture sets drawn >12 h apart
- All of 3 or majority of ≥4 separate blood cultures, with first & last drawn at least 1 hr apart

C. Single positive blood culture for *Coxiella burnetii* or phase-I IgG antibody titer of >1:800

2.Evidence of endocardial involvement: any one

A. Positive echocardiogram

- Oscillating intracardiac mass on valve OR
- Abscess OR
- New partial dehiscence of prosthetic valve

B. New valvular regurgitation

Diagnosis (Modified Duke Criteria)

Minor Criteria

1. **Predisposition:** predisposing heart conditions or IV drug use
2. **Fever** ≥ 38.0°C (≥100.4°F)
3. **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial hemorrhage, conjunctival hemorrhages or Janeway lesions
4. **Immunologic phenomena:** glomerulonephritis, Osler's nodes, Roth's spots or rheumatoid factor
5. **Microbiologic evidence:** positive blood culture but not meeting major criterion as noted previously or serologic evidence of active infection with organism consistent with infective endocarditis

Definite endocarditis if followings are present:

- Two major criteria or
- One major criterion & three minor criteria or
- Five minor criteria

Blood Cultures

- Critical for diagnosis, AST, planning of treatment
- Collected before antibiotic therapy
- Two blood culture sets- collected at interval of >12hr between 1st & 2nd set
- Alternatively- ≥3 blood culture sets collected over 1hr (30mins gap between 1st & 2nd set and 30mins gap between 2nd & 3rd set)
  *__Blood culture set__- blood collected from single venipuncture site & divided into 2 bottles (pair of bottles)

Non-blood-culture Tests

- **Serologic tests**: *Brucella, Bartonella, Legionella, Chlamydophila psittaci, C.burnetii*
- **Culture**: isolation of pathogens in *vegetations*
- **Microscopic examination**: special stains (PAS-*Tropheryma whipplei*)
- Direct **fluorescence antibody** techniques
- **PCR** to recover unique microbial DNA or 16S rRNA, when sequenced- allows identification of etiological agent
- **Echocardiography**: allows anatomic confirmation of IE, sizing of *vegetations*, detection of intra-cardiac complications, assessment of cardiac function

Treatment- Infective endocarditis

1. Regimen for *S. aureus* IE

- For native valve IE:

➢ For MSSA: Cloxacillin or nafcillin- for 6 weeks

➢ For MRSA: Vancomycin- for 6 weeks

- For prosthetic valve IE:

➢ Above regimen + rifampin (6 wks) & gentamicin (2 wks)

2. Regimen for viridans streptococci & *S. gallolyticus* IE

- For native valve IE: Penicillin or ceftriaxone- for 4 wks
- For prosthetic valve IE: Penicillin or ceftriaxone + Gentamicin for 6 weeks

Treatment- Infective endocarditis

3. For HACEK endocarditis

- Ceftriaxone or ciprofloxacin- for 4 weeks
- Prosthetic valve IE- treatment extended for 6 weeks

➢ Therapeutic drug monitoring: performed to maintain optimum antibiotic level in serum

❑ Vancomycin dosage: 15-20 mg/kg, q8-12h. Target trough concentration of 15-20 µg/mL need to be maintained Vancomycin should avoided if MIC >1 µg/mL

❑ Gentamicin dosage: 1 mg/kg, q8h IV. Used for synergy; peak levels need not exceed 4 µg/mL & troughs should be <1 µg/mL

Staphylococcal endocarditis

- *S. aureus*- common cause of IE; usually runs acute course
- *S. aureus* IE presents with larger *vegetations* (>10 mm)→ associated with features of septic embolization (breaking of *vegetations* leading to formation of emboli)
  e.g. subungual hemorrhage, Osler's nodes
- ➢ Cerebrovascular emboli- cause strokes or occasionally encephalopathy
- ➢ Embolization risk- higher for mitral valve IE
- Coagulase-negative staphylococci (*S. epidermidis*) increasingly associated with prosthetic valve endocarditis (68-85% of cases) & majority- methicillin resistant

Viridans Streptococci

- Commensals of mouth & upper respiratory tract
- Non-pathogenic, occasionally cause diseases-

➢ **Subacute bacterial endocarditis** (SABE): *S.sanguinis* enter blood to cause transient bacteremia (chewing, tooth brushing, dental procedure)→ predilection to cause endocarditis

➢ Dental caries

➢ Cancer patients: cause prolonged bacteremia

➢ S. milleri group: produce suppurative infections

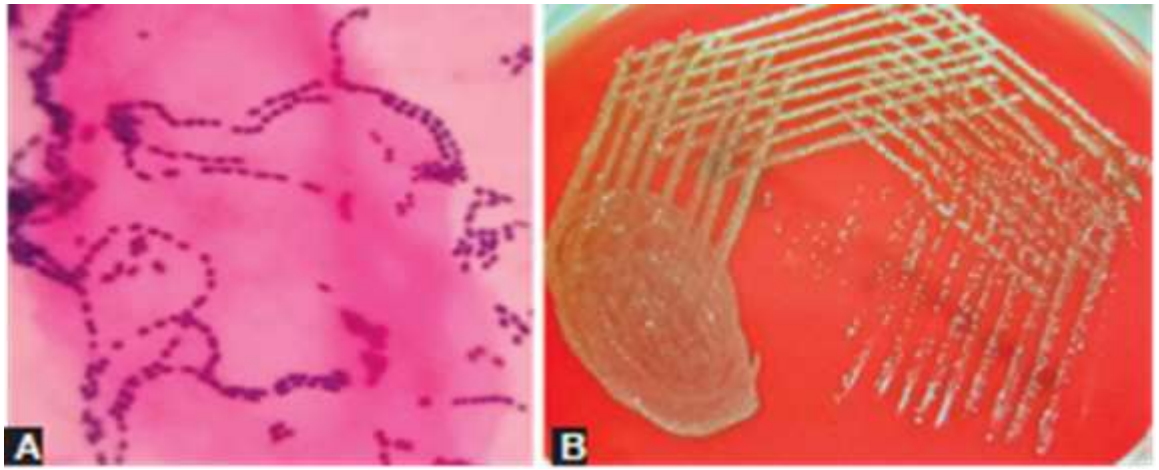
Viridans Streptococci

- **Laboratory Diagnosis**:

➢ Gram stain- GPC long chains

➢ BA- minute α-haemolytic green coloured colonies

➢ Species identification- MALDI-TOF



A. Gram-positive cocci in long chains
B. α hemolytic colonies on blood agar

Viridans Streptococci

- **Treatment**: sensitive to penicillin EXCEPT neutropenic patients with bacteremia- vancomycin drug of choice

➢ Resistant isolates- peni+genta (low level resistance) & ceftriaxone/vancomycin (high level resistance)

Nutritionally Variant Streptococci

- Abiotrophia & Granulicatella spps- nutritionally variant streptococci
- Require vitamin B (pyridoxal) in culture medium for growth
- Normal inhabitants of oral cavity, cause endocarditis
- **Diagnosis**: recovered in automated blood cultures- BacT/ALERT. Multiple blood cultures & prolonged incubation necessary
  - GPC, identification- MALDI-TOF
  - Fail to grow when subcultured on solid media
  - Produce satellite colonies near colonies of "helper" bacteria (*S. aureus* streak line)- satelliting streptococci
- **Treatment**: Combination- penicillin plus gentamicin

S. gallolyticus endocarditis

- *S. gallolyticus* (formerly *S. bovis*)- group D Streptococcus, commensal in intestine of animals
- In humans- occasionally causes bacteremia, subacute endocarditis, associated with colorectal cancer or polyps

- Penicillin- drug of choice

HACEK endocarditis

- Group of highly fastidious, slow-growing, capnophilic (5-10% CO_2), gram-negative bacteria- commensal in oral cavity
- Associated with local infections of mouth & systemic infections- bacterial endocarditis

➢ *Haemophilus parainfluenzae*

➢ Aggregatibacter species: *A.actinomycetemcomitans, A.aphrophilus, A.paraphrophilus*

➢ *Cardiobacterium hominis*

➢ *Eikenella corrodens*

➢ *Kingella kingae*

HACEK endocarditis

- Accounts for 3% of total IE cases
- Subacute course
- Occurs in patients with preexisting valvular defects or patients undergoing dental procedures
- Aortic & mitral valves- commonly affected

HACEK endocarditis

- **Laboratory diagnosis**:

➢ Culture: blood cultures performed on automated systems BacT/ALERT
Identification by MALDI-TOF
Highly fastidious- multiple blood cultures, prolonged incubation up to 1 week

➢ Molecular methods:

✓ Broad-range bacterial PCR- followed by sequencing

✓ Multiplex PCR or multiplex real-time PCR

HACEK endocarditis

- **Treatment**:

➢ Ceftriaxone (2 g/day): drug of choice- except *Eikenella corrodens*- ampicillin

➢ Quinolones: for β-lactamase producer

➢ <u>Duration of treatment</u>:

✓ Antibiotics: 4 weeks for native valve IE & 6 weeks for prosthetic-valve endocarditis

Other Infections of CVS

- Infections of heart:
  - Myocarditis
  - Pericarditis
  - Pericardial effusion
- Infections of blood vessels:
  - Mycotic aneurysm
  - Infective endarteritis
- Device related infections:
  - CRBSI
  - Suppurative thrombophlebitis

Acute Rheumatic Fever

- Multisystem disease: occurs in people previously infected with streptococcal (group A) sore throat→ result of autoimmune reaction
- All manifestations resolve completely: except cardiac valvular damage- rheumatic heart disease (RHD)
- **Pathogenesis**:

➢ Disease of children age 5-14 years

➢ Rare in more than 30 years

➢ RHD- F > M

➢ Recurrent episodes- in adolescents & young adults

ARF- Pathogenesis

- ARF results following URTI with group A streptococci (by M-serotypes 1, 3, 5, 6, 14, 18, 19, 24, 27, 29)
- Genetic predisposition- play role; people with HLA-DR7 & HLA-DR4 more susceptible
- **Pathogenesis** unclear-

➢ Autoimmune theory: molecular mimicry- antibodies targeted against streptococcal M-protein cross-react with human tissue antigens (heart, joint)→ cross reacting antibodies bind to valvular endothelium→ damage to heart valve

➢ Cytotoxic theory

ARF- Clinical Manifestations

- Appear after period of ~3 weeks following Gr-A streptococcal infection
- Prior streptococcal infection- subclinical (common) or sore throat
- ARF- affects heart, joints, skin & brain
- Common manifestations:

➢ Migrating polyarthritis
➢ Pancarditis
➢ Subcutaneous nodules
➢ Chorea (Sydenham's)
➢ Erythema marginatum

Diagnostic criteria: Rh. Fever- Modified (Revised) Jones criteria (2015)

- Based on presence of combination of
  - ➢ Typical clinical features
  - ➢ ECG findings
  - ➢ Laboratory findings (ESR, CRP)

Rh. Fever- Modified Jones Criteria

Major criteria	
Low-risk population	**High-risk population**
Carditis (clinical/ subclinical)	Carditis (clinical/ subclinical)
Arthritis- only polyarthritis	Arthritis- monoarthritis or polyarthritis
	Polyarthralgia
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules

Rh. Fever- Modified Jones criteria

Minor criteria	
Low-risk population	**High-risk population**
Polyarthralgia	Monoarthralgia
Hyperpyrexia (≥ 38.5ºC)	Hyperpyrexia (≥ 38.0ºC)
ESR ≥ 60 mm/h &/or CRP ≥ 3.0 mg/dL	ESR ≥ 30 mm/h &/or CRP ≥ 3.0 mg/dL
Prolonged PR interval	Prolonged PR interval
Diagnostic criteria	
Initial ARF	2 major OR 1 major + 2 minor
Recurrent ARF (with reliable past history of ARF/RHD)	2 major OR 1 major + 2 minor OR 3 minor criteria

Treatment

- Penicillin: drug of choice- orally (penicillin V or amoxicillin for 10 days) or intramuscularly single dose of 1.2 million units of benzathine penicillin G

- Supportive treatment (aspirin)- for arthritis, arthralgia, fever

Prevention

- **Primary Prevention**:

➢ Timely, complete treatment of Gr-A streptococcal sore throat with antibiotics (penicillin) within 9 days of sore throat onset

- **Secondary Prevention**:

➢ Long-term penicillin prophylaxis: to prevent recurrences

- Drug of choice: intramuscular benzathine penicillin G given every 4 weeks
- Penicillin allergy: erythromycin (250 mg, twice day)
- Duration: depends upon underlying carditis