Infective Endocarditis:

→ microbial invasion of heart valves or mural endocardium resulting in formation of friable bulky vegetations
(Vegetations: composed of mass of platelets, fibrin, microbes, scanty inflammatory cells)

Acute Endocarditis	Subacute Endocarditis
Rapid onset	Slow onset
Involves normal cardiac valves	Involves previously damaged heart valves
High virulence organisms eg: Staph. aureus	Low virulence organisms eg: viridans streptococci
Causes substantial morbidity & mortality even with appropriate antibiotic therapy	Gradually progressive course; most patients recover after antibiotic therapy
Less common	More common

Etiological Agents: (depending on primary portal of entry into bloodstream)

→ Oral cavity: Viridans streptococci
→ Skin: Staphylococci
→ Upper Respiratory Tract: HACEK organisms
→ GI tract: Streptococcus gallolyticus & enterococci

HACEK: fastidious gram -ve organisms
- Haemophilus species
- Aggregatibacter sp.
- Kingella sp.
- Cardiobacterium hominis
- Eikenella corrodens

Pathogenesis:

Underlying Risk factors:
→ Underlying cardiac defect (Congenital valvular disease)
→ use of intravenous catheter
→ Prosthetic valve replacement

Endothelial Injury: endothelium is generally resistant to infection by most bacteria & to thrombus formation
∴ IE more commonly develops on a defective valve
→ predisposing cardiac abnormalities produce turbulence to blood flow which damages cardiac endothelium.
→ damage to endothelium causes deposition of platelets & fibrin ⇒ Nonbacterial thrombotic endocarditis (NBTE).

Colonization: thrombus serves as a sight for bacterial attachment

Formation of Vegetations: after colonization, endothelial surface gets covered with a protective layer of fibrin & platelets which serves as a substrate for further bacterial multiplication
(Vegetation = platelets + fibrin + inflammatory cells + microbes)

Metastasis: bacteria from vegetations enter the bloodstream & metastasize to distant sites

Clinical Manifestations:

Cardiac manifestations: new/worsened regurgitant murmur

Non-Cardiac manifestations: fever, chills, sweats, anorexia, weight loss, myalgia, arthralgia, splenomegaly, petechiae, clubbing, Osler's nodes, subungual haemorrhages, Janeway lesions

Laboratory manifestations: anemia, leucocytosis, microscopic hematuria, elevated ESR/CRP/rheumatoid factor.

Modified Duke Criteria:

Major Criteria:

① Positive blood culture
- → typical IE organism isolated from two separate blood cultures
- → persistently +ve blood culture with agents other than typical IE organisms
- → single +ve blood culture for Coxiella burnetti or phase I IgG Ab titer > 1:800

② Evidence of endocardial involvement
- → +ve echocardiogram
- → new valvular regurgitation

Minor Criteria:

① **Predisposition:** to heart condition or IV drug use

② **Fever:** ≥ 100.4 °F

③ **Vascular phenomena:** major arterial emboli, septic pulmonary infarcts, mycotic aneurysm, intracranial haemorrhage

④ **Immunologic phenomena:** glomerulonephritis, Osler's nodes, Roth's spots, rheumatoid factor

⑤ **Microbiologic evidence:** +ve blood culture but not meeting major criterion

Definitive endocarditis: 2 major / 1 major + 3 minor / 5 minor criteria present

Lab Diagnosis:

Blood cultures: 2 blood culture sets collected at an interval of > 12 hr **OR** 3 blood culture sets collected at 30 min intervals

Non-Blood-Culture Tests: serological tests, direct fluorescence, PCR

Echocardiography.

Treatment: for S. aureus IE

Native valve IE:

- **MSSA:** Cloxacillin or nafcillin for 6 weeks
- **MRSA:** Vancomycin for 6 weeks

Prosthetic Valve IE: above regimen + rifampin (6 weeks) + gentamicin (2 weeks)

for HACEK endocarditis: ceftriaxone/ciprofloxacin (for 4 weeks in normal valve IE) 6 weeks in prosthetic valve IE)

Native valve endocarditis: • Staph. aureus • Viridans streptococci

Prosthetic valve endocarditis: most commonly caused by CoNS

→ Early (within 12 months of valve replacement ; due to intra-operative contamination)

→ Late (after 12 months of valve replacement)

Acute Rheumatic Fever: (ARF)

→ multisystem disease (S. pyogenes)
→ occurs in people previously infected with streptococcal (Group A) sore throat due to autoimmune reaction

Pathogenesis: mainly affects children of 5–14 years (rare > 30 years of age)
→ RHD (rheumatic heart disease) more commonly affects females
→ people with HLA-DR7 & HLA-DR4 appear to be more susceptible

Autoimmune theory: Based on molecular mimicry ⇒ antibodies targeted against streptococcal M antigens cross react with human tissue antigens (eg: heart & joint)

Cytotoxic theory: streptococcal toxins (pyrogenic toxin) & enzymes (streptolysin O) are directly toxic to human heart.

Clinical Manifestations: usually appear 3 weeks after group A streptococcal infection
→ affects heart, joints, skin, brain

- **Migrating polyarthritis:** hot, swollen, red or tender joints; moves from one joint to another over hours
- **Pancarditis:** affects endocardium, myocardium &/or pericardium
- PR interval lengthening
- **Subcutaneous nodules:** painless small mobile lumps beneath the skin overlying bony prominences
- **Sydenham's chorea:** abnormal involuntary movements
- **Erythema marginatum:** pink macular rashes that appear & disappear before examiner's eye.

Jones Criteria:

Major Criteria

Low-Risk population	High-Risk population
Carditis	Carditis
Arthritis (polyarthritis)	Poly/mono arthritis
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules

Minor Criteria

Low-Risk population	High-Risk population
Polyarthralgia	Monoarthralgia
Hyperpyrexia (> 100.4°F)	Hyperpyrexia (> 100.4°F)
ESR > 60 mm/hr &/or	ESR ≥ 30 mm/hr &/or
CRP ≥ 3 mg/dl	CRP ≥ 3 mg/dl
Prolonged PR interval	Prolonged PR interval

Diagnosis:

- **Initial ARF:** 2 major / 1 major + 2 minor
- **Recurrent ARF:** 2 major / 1 major + 2 minor / 3 minor

Treatment: DOC = Penicillin

Prevention:

Primary Prevention: timely & complete treatment of group A streptococcal sore throat with antibiotics within 9 days of sore throat onset

Secondary Prevention: Long-term penicillin prophylaxis with penicillin in patients with ARF to prevent recurrence. (Alternatives: Benzathine penicillin G1 or erythromycin)

- ARF without carditis: for 5 years after last attack
- ARF with carditis but no residual valvular disease: for 10 years after last attack
- ARF with persistent valvular disease: for 10 years after last attack or lifelong.

Sepsis: life-threatening organ dysfunction caused by a dysregulated host response to infection.

SOFA Score (Sepsis-related Organ Failure Assessment):

1. Respiratory system: PaO_2 / FiO_2
2. Coagulation system: Platelet count
3. Liver: Serum bilirubin
4. Cardiovascular: Mean arterial pressure (MAP)
5. CNS: Glasgow Coma scale score
6. Renal: Serum creatinine & urine output

} organ dysfunction = change of ≥ 2 in total SOFA score

Glasgow Coma Scale:

Eye Opening Response (E)
- 4 - Spontaneously
- 3 - to speech
- 2 - to pain
- 1 - no response

Verbal Response (V)
- 5 - Oriented to time, place & person
- 4 - Confused
- 3 - Inappropriate words
- 2 - Incomprehensible
- 1 - No response

Motor Response (M)
- 6 - Obeys command
- 5 - moves to localised pain
- 4 - flex to withdraw from pain
- 3 - Abnormal flexion
- 2 - Abnormal extension
- 1 - No response

Best Score: 15
Comatosed: ≤ 8
Unresponsive: 3

Head Injury
Mild: 13-15
Moderate: 9-12
Severe: 3-8

Brucellosis: (Contagious febrile illness) aka undulant fever / Malta fever

→ human infection is associated with occupational/domestic exposure to infected animals or their products.

Brucella: obligate aerobic, fastidious, gram -ve coccobacillus

→ family Brucellaceae

- B. melitensis
- B. abortus
- B. suis
- B. canis

Antigenic Structure: 2 major lipopolysaccharide (LPS) antigens — M, A.

→ In B. melitensis: M is predominant

In B. abortus: A is predominant

In B. suis: contains either M or A antigen

Pathogenesis:

Transmission: Zoonotic (from infected animals to man)

- **Direct contact:** of abraded skin/mucosa with infected animal/animal product
- **Food-borne:** by ingestion of unpasteurized milk/dairy products or undercooked meat
- **Air-borne**
- **Person-to-person:** extremely rare; through breast milk / blood transfusion / tissue transplantation

Spread: spread of organisms through bloodstream & dissemination to various organs

Organs involved: Organs of reticuloendothelial system: lymph nodes, spleen, liver, bone marrow

→ Placenta, musculoskeletal tissues, genitourinary organs

Local Tissue Response: initial neutrophilic infiltration → replacement with chronic inflammatory cells → granuloma formation

Intracellular Survival: with the help of cell-wall LPS

Host-Immune Response: CMI; $T_{H}1$ cells produce IFN-γ

Clinical Manifestations: incubation period ⇒ 1 week - several months

Classic Triad: fever with profuse night sweats + arthralgia/arthritis + hepatosplenomegaly

→ foul-smelling perspiration

Typhoid-like illness

Undulating Fever: in between febrile periods, there are afebrile periods

Musculoskeletal Symptoms: Vertebral osteomyelitis (in lumbar & lower thoracic vertebrae), septic arthritis

Nonspecific Symptoms: abdominal pain, headache, rash, fatigue, weight loss, vomiting, cough

CNS: depression, lethargy

CVS: endocarditis affecting aortic valve

Genitourinary manifestations: epididymo-orchitis, prostatitis, salpingitis, pyelonephritis

Endemicity: Mediterranean zone, Eastern Europe, Central Asia

Lab Diagnosis:

Specimen: blood, bone marrow, etc.

Blood Culture: → Castaneda's biphasic media (BHI broth/agar)

→ Automated ⇒ BACTEC or BacT/ALERT

Culture Smear & Motility Testing: non-capsulated, small, gram -ve coccobacilli, non-motile.
Identification: catalase & oxidase +ve
Antibody Detection:
Standard Agglutination Test (SAT): tube agglutination test detecting Ab against LPS Ag (IgM)
Tests to Detect IgG: 2-mercaptoethanol SAT test, ELISA
Molecular Methods: PCR (using primers for 16S-23S rRNA operon), FilmArray Bio Threat Panel (automated multiplex PCR)

Treatment:

Standard regimen: Gentamicin (7 days) + Doxycycline (6 weeks)
WHO regimen: Rifampin (6 weeks) + Doxycycline (6 weeks)
For CNS involvement: Ceftriaxone is added

Prevention:

In animals: – test & slaughter active cases
– live attenuated vaccine
In humans: – use of pasteurized milk & properly cooked food
– live attenuated vaccine

HIV/AIDS:

Retrovirus: RNA viruses ; possess a unique enzyme reverse transcriptase

Family Retroviridae: – Genus Lentivirus (HIV 1 & 2)
– Genus Deltaretrovirus (HTLV-1)

Structure: spherical ; 80-110 nm in size

Envelope:

Lipid part: host cell-membrane derived

Protein part: gp 120 , gp 41

Nucleocapsid: icosahedral symmetry

→ 2 identical copies of ss RNA

→ Viral enzymes: reverse transcriptase, integrase, protease

Genes:

- 3 structural genes : gag, pol, env
- 6 nonstructural (regulatory) genes

gag gene: codes for core & shell of virus
- p18 – matrix/shell antigen
- p24 & p15 – core antigens

pol gene: codes for viral enzymes

env gene: codes for envelope glycoprotein (gp 120, gp 41)

Essential regulatory genes: tat , nef, rev

Accessory regulatory genes: vif , vpr , vpu

→ high rates of mutation ⇒ due to error prone nature of reverse transcriptase
[env = most mutated]

Pathogenesis:

Transmission:

- Sexual mode : anal intercourse has higher risk of transmission than vaginal intercourse
- Blood transfusion
- Percutaneous/mucosal: needle stick injury , IV drug abuse
- Perinatal : during pregnancy / delivering / breast feeding

Receptor Attachment:

→ binding of gp 120 to CD4 receptor on helper T cells & CCR5 molecules on macrophages

→ dendritic cell-specific lectin receptor present in skin & mucosal surfaces can bind to HIV-1

→ Mutations in CCR5 result in blockade of HIV entry into cells ; found in Europe & Western Asia

Replication:

Attachment of receptor & co-receptor to gp120 → fusion to host cell → uncoating of HIV capsid → release of 2 copies of ssRNA & viral enzymes → viral reverse transcriptase converts ssRNA to ssDNA → RNA is degraded by viral endonucleases → ssDNA replicates to form dsDNA → DNA transcription to form some viral components → Pre-integration complex transported into host nucleus → viral dsDNA is integrated into host DNA to form provirus

Natural Course of Disease: 5 stages

① **Acute Retroviral Syndrome:** HIV is carried to lymph nodes & lymphoid tissue where they multiply inside T cells
→ HIV spills into bloodstream to cause primary viremia ⇒ initial flu-like illness
→ significant drop in number of circulating CD4 T cells

② **Clinical Latency:** adequate immune response
→ CD4 T cell count becomes normal but HIV continues to multiply in lymph nodes
→ few months to 30 years

③ **Persistent Generalized Lymphadenopathy (PGL):** enlarged lymph node of >1 cm in 2 or more non-contiguous sites that persist for at least 3 months

④ **AIDS-related Complex:** fall in CD4 T cell count
→ unexplained diarrhoea, weight loss (>10%), fatigue, malaise, night sweat, oral thrush

⑤ **Full-blown AIDS:** advanced end-stage HIV; rapid fall in CD4 T cell count (<200 cell/μL)
→ **Opportunistic infections:** secondary to immune suppression
→ lymphoid tissue is totally destroyed & replaced by fibrous tissue.

Epidemiology: infected people are the only reservoir host

Extremely high-risk group: female sex worker, IV drug abusers, homosexual men
Moderately high-risk group: health care workers, recipients of blood transfusion

Opportunistic Infections: TB is most common

Fungal: Candidiasis (oral thrush), Pneumocystis jirovecii
Viral: Herpes simplex mucosal lesions, CMV retinitis
Parasitic: Cryptosporidium parvum diarrhoea, Toxoplasma encephalitis, Strongyloides stercoralis hyperinfection syndrome.

NACO: AIDS-free India by 2030.
Window period: following infection, antibodies appear in serum only after a period of 3-12 weeks

Laboratory Diagnosis:

3 C's while HIV testing: Consent, Confidentiality, Counseling

Screening Tests for Ab Detection:
- ELISA (takes 2-3 hours)
- Rapid/Simple Test (takes < 30 mins)

Supplemental Tests for Ab Detection:
- Western Blot Assay
- Line Immunoassay

Confirmatory Tests:
- p24 core Antigen detection
- viral culture – by co-cultivation technique (culture of peripheral blood mononuclear cells)
- viral RNA detection (gold standard) ⇒ best tool for diagnosis of HIV during window period
- HIV DNA detection by PCR

Non-Specific Immunological Tests:
- Low CD4 T-cell count
- Hypergammaglobulinemia
- Altered CD4:CD8 T cell ratio

Diagnosis of Pediatric HIV:
→ ELISA cannot differentiate between baby's IgG or normally transferred maternal IgG
→ HIV DNA PCR is used.

Treatment:

- Clinical goals: prolongation of life, improvement of quality of life
- Virological goals: greatest possible reduction in viral load
- Immunological goals: immune reconstitution
- Transmission goals: Reduction in transmission

Highly Active Antiretroviral Therapy (HAART)