BLOODSTREAM AND CARDIOVASCULAR SYSTEM INFECTIONS

INFECTIVE ENDOCARDITIS

Microbial invasion of heart valves / mural endocardium

⇓

formm of vegetations

Pathogenesis :

→ Predisposing factors : Cardiac defect (eg. mitral regurgitation)

Intravenous catheter

Prosthetic valve surgery

⇓

→ Endothelial injury : Damage to the endothelial surface

⇓

deposition of platelets & fibrin → THROMBUS

⇓

→ Colonization : During transient bacteremia, bacteria adhere to thrombus

⇓

→ Formm of vegetations : deposition of platelets, fibrin, inflammatory cells surrounding entrapped organisms

→ metastasis : metastasize to distant sites

Etiological agents :

- Staphylococcus aureus
- Coagulase - negative staphylococci
- Streptococci

- Enterococci
- Pneumococci
- Enterobacteriaceae
- Pseudomonas spp.
- Candida species
- Diphtheroids

Clinical manifestations :

- CARDIAC MANIFESTATIONS : worsened regurgitant murmur
- NON-CARDIAC MANIFESTATIONS : fever, chills & sweats, anorexia, weight loss, myalgia, arthralgia, splenomegaly, clubbing, neurological manifestations
- LABORATORY FINDINGS : Anemia, leucocytosis, elevated ESR, CRP

Diagnosis → Modified Duke criteria

Table 28.3: Modified Duke criteria for the clinical diagnosis of infective endocarditis.

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* or enterococci) or
   B. Persistently positive blood culture with agents other than typical IE organisms:
      - At least two blood culture sets drawn >12 h apart; or
      - All of 3 sets or a majority of ≥4 separate blood culture sets, with first and last drawn at least 1 h 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

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[a] or serologic evidence of active infection with organism consistent with infective endocarditis

Definite endocarditis if the followings are present:
- Two major criteria or
- One major criterion and three minor criteria or
- Five minor criteria

ACUTE RHEUMATIC FEVER

Multisystem disease that occurs in people previously affected with Streptococcal (Group A) sore throat, as a result of an AI reaction

Aetiological agent → Group A Streptococcus (S. pyogenes)

Pathogenesis

- mainly children affected

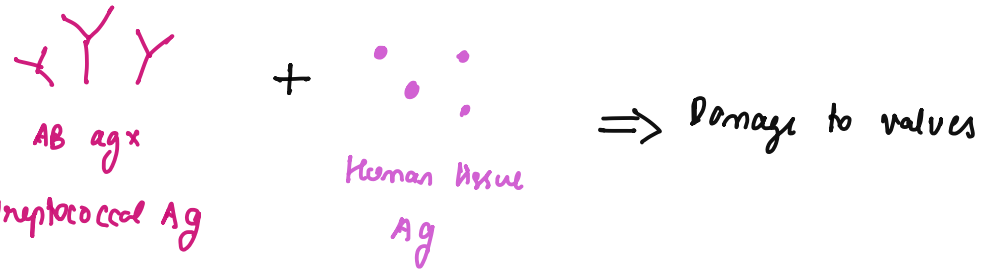
a) URTI
   - ↳ ARF occurs following URTI with grp A Streptococci

b) Genetic predisposition
   - ↳ People with HLA-DR7 & HLA-DR4 more susceptible

c) AI theory
   - ↳ Based on "molecular mimicry"

AB targeted against Streptococcal Ag cross react with human tissue Ag

→ then bind to valvular endothelium → damage



Clinical manifestations

→ occurs after 3 weeks following Strept. infection

a) MIGRATING POLYARTHRITIS : Joints become hot, swollen, red, tender.

b) PANCARDITIS : Affects endo, peri or myocardium

c) SUBCUTANEOUS NODULES : Painless, small, mobile bumps beneath skin

d) CHOREA : Involuntary abnormal movts

e) ERYTHEMA MARGINATUM : Pink macular rashes

Diagnosis : Jones Criteria

Table 28.4: Diagnostic criteria for rheumatic fever—modified Jones criteria (2015).

Major criteria	
Low-risk population	**High-risk population**
Carditis (clinical or subclinical)	Carditis (clinical or subclinical)
Arthritis—only polyarthritis	Arthritis —monoarthritis or polyarthritis
	Polyarthralgia
Chorea	Chorea
Erythema marginatum	Erythema marginatum
Subcutaneous nodules	Subcutaneous nodules
Minor criteria	
Low-risk population	**High-risk population**
Polyarthralgia	Monoarthralgia
Hyperpyrexia (≥ 38.5°C)	Hyperpyrexia (≥ 38.0°C)
ESR ≥ 60 mm/h and/or CRP ≥ 3.0 mg/dL	ESR ≥ 30 mm/h and/or CRP ≥ 3.0 mg/dL
Prolonged PR interval	Prolonged PR interval
Diagnostic criteria	
Initial ARF	Two major or One major + two minor
Recurrent ARF with a reliable past history of ARF/RHD)	Two major or One major + two minor or Three minor criteria

Prevention :

1° prevention → Complete treatment of grp A Strept. sore throat (penicillin)

2° prevention → long term penicillin prophylaxis indicated to prevent recurrences

→ DOC for 2° prophylaxis : Im benzathine penicillin (in allergy → Erythromycin)

TYPHOID

Typhoidal Salmonella : S. typhi & S. paratyphi

↳ Restricted to human hosts ⇒ Enteric fever

Table 30.1: Differences between somatic (O) and flagellar (H) antigen.

Somatic (O) antigen	Flagellar (H) antigen
It is a part of cell wall lipopolysaccharide (LPS)	Made up of protein flagellin It confers motility to the bacteria
In Widal test, O antigen of *S. Typhi* is used	In Widal test, H antigens of *S. Typhi*, *S.* Paratyphi A and B are used
It is less immunogenic	It is more immunogenic
O antibody appears early, disappears early: indicates recent infection	H antibody appears late, disappears late: indicates convalescent stage
When O antigen reacts with O antibody forms compact, granular, chalky clumps • Agglutination takes place slowly • Optimum temperature for agglutination is 55°C	When H antigen reacts with H antibody forms large, loose, fluffy clumps • Agglutination takes place rapidly • Optimum temperature for agglutination is 37°C
Serogrouping of salmonellae is based on the O antigen	Serogroups are differentiated into serotypes based on H antigen

Pathogenesis :

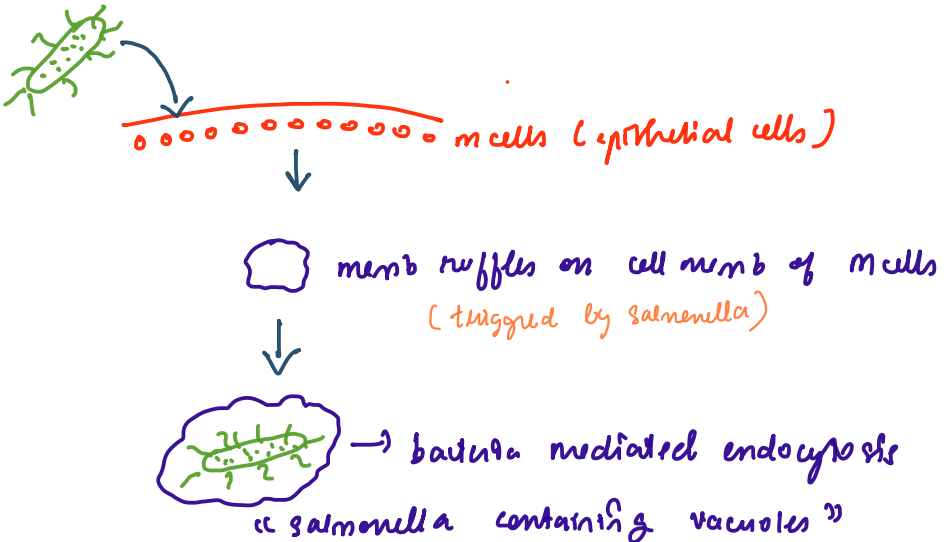
→ Transmitted by oral route

→ Ingestion of contaminated food or water

o) Infective dose → $10^3 - 10^6$ bacilli

o) Risk factors → decrease in stomach acidity (*H. pylori* infection)

" in intestinal integrity



↓

Reach submucosa

↓

Phagocytosed by monophages

↓

S. typhi becomes susceptible to lysosomal enzymes of mp (by altering its LPS)

↓

Spread via lymphatics

↓

Blood stream

↓

further multiplications (in reticuloendothelial tissues & in other organs)

↓

2° bacteremia

Clinical manifestations

- Fever – "step ladder pattern of fever"
- Other symptoms : Headache, chills, cough, sweating, arthalgia
- Rashes (rose spots)
- Intestinal manifestations → abdominal pain, nausea, vomiting, constipation
- Hepatosplenomegaly, epistaxis
- Complications → GIT bleeding, intestinal perforations
- Neurological manifestations → meningitis, ataxia, neuropsychiatric manifest.
- Coated tongue, bradycardia

Laboratory diagnosis

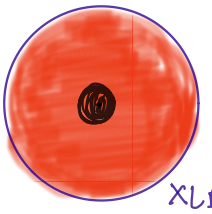
1) SPECIMEN COLLECTION

- Blood / BM culture (1st week)
- Serum for serology (2nd - 3rd week)
- urine & stool culture (3rd/4th weeks)

2) CULTURE ISOLATION

- Blood & BM (1st week)
  - → conventional : BHI agar / broths
  - → Automated : BACTEC / BACT / ALERT
    - ⇒ non-hemolytic moist colonies
- Stool culture (3rd/4th weeks)
  - → enrichment broths : Selenite F broths, gram -ve broths
  - → Low selective medium : MacConkey agar (NLF)
    - round, translucent, pale
  - → Highly selective media : XLD, DCA etc.
    - NLF, pale colonies with black centres
    - red colonies + black centre
- Urine culture
  - → MacConkey agar

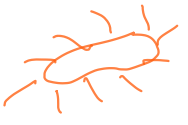
Colony appearance :
Blood agar → non hemolytic moist colonies
MacConkey agar → round, translucent, pale, NLF



BLACK CENTRE - ENTERIC FEVER

3) CULTURE SMEAR & MOTILITY

Motile & gram negative bacilli (non-capsulated)



non-sporing, non-capsulated - motile with peritrichous flagella

4) IDENTIFICATION

By conventional biochemical tests or automated systems

(MALDI-TOF or VITEK)

→ Catalase +, oxidase −, ICU −

Salmonella - Salmon

5) SLIDE AGGLUTINATION TEST

To confirm the serotype

6) Serum AB DETECTION (widal TEST) — TUBE AGGLUTINATION TEST

2-3 weeks of illness — "tube agglutination test" detects AB (serum) agx the Ag of ST & SPT

AB detected agx TO, TH, AH, BH Antigens

In S. typhi infection → ↑ TO & TH ABs

In S. Paratyphi A infection → ↑ TO & AH ABs

In S. Paratyphi B infection → ↑ TO & BH ABs

Result & interpretations

→ O antibodies : OAB + OAg → granular chalky clumps

→ H antibodies : HAB + HAg → cotton woolly clumps

7) Ag DETECTION (SERUM & URINE)

→ By ELISA

8) MOLECULAR METHODS

PCR detecting flagellin gene

9) NONSPECIFIC FINDINGS

eg. Neutropenia

10) ANTIMICROBIAL SUSCEPTIBILITY TESTING

WIDAL TEST

- 2-3 weeks of illness
- Tube agglutination test
- Detects AB in patient's serum against ST & SPT

Ag used : (O) Ag of S. typhi (TO)
(H) Ag of S. typhi (TH)
(H) Ag of S. Paratyphi (A) (AH)
(H) Ag of S. Paratyphi (B) (BH)

Procedure : Patient serum + 4 diff Ag (TO, TH, AH, BH)

Result : Read using concave mirror

2 AB

O AB → granular chalky clumps
H AB → cotton woolly clumps

Interpretation :

In S. typhi infection : ABs agx TO & TH ↑
In S. Paratyphi A : ABs agx TO & AH ↑
In S. Paratyphi B : ABs agx TO & BH ↑

False negative :

- In early stage (1st week)
- Due to prior antimicrobial therapy

False positive :

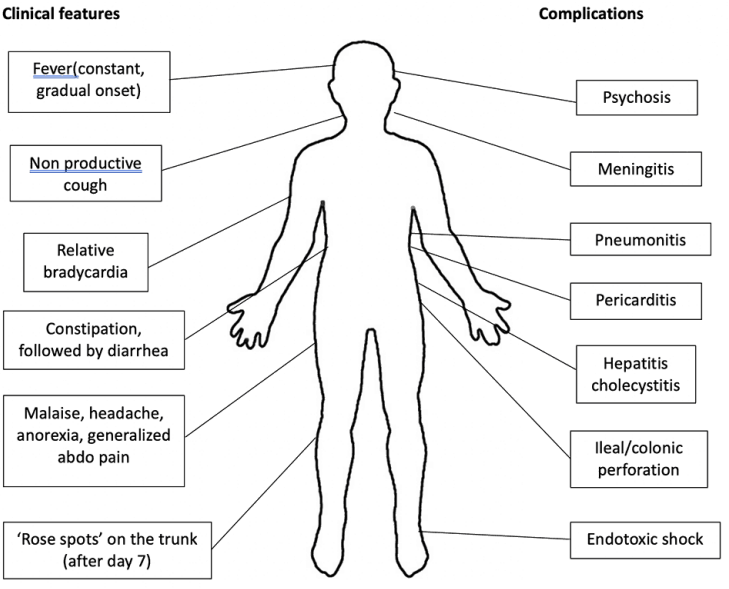
- Anamnestic response → transient rise in titres → Due to unrelated infections (eg. malaria, dengue)

  Widal in titres in anamnestic response are transient that usually falls after 1 week, whereas in true infection, titre increases by 4 fold after 2 weeks.

  transient - കുറച്ച് നേരത്തേക്ക് മാത്രം ഉള്ളത്

- Person with prior immunisation.

  കുത്തിവെച്ചതിനു ശേഷം കൂടും പിന്നെ താഴും (after 1 week)



Treatment : DOC → Ceftriaxone 1-2g/day, IV for 10-14 days

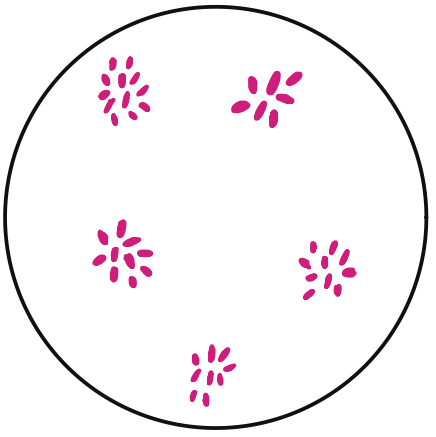
Alternative → Azithromycin.

Vi-CPS, typhoid, Parenteral TAB vaccine } Vaccines for typhoid

BRUCELLOSIS

Brucella → Obligate aerobic (fastidious), gram -ve cocobacillus

Bruce Wayne



melitensis

B. melitensis

Pathogenesis :

"B. melitensis" - most pathogenic species

- Transmission → ZOONOTIC (Infected animals → man) → Corbella bunneti
  - → food borne : m/c → Batman
  - → Direct contact
  - → Air borne
  - → Person to person
- Spread → through bacteremia → Initial site → bloodstream → ∴ bacteremia → organs (because it is a BS infection)
- Organs involved → 1° infect Reticuloendothelial system
- Local tissue response → initially, neutrophilic infiltration occurs, later on replaced by chronic inflammatory cells leading to granuloma formation
- Intracellular survival → cell coat - LPS appears to be the major virulence factor (key role) → Batman costume

• Host immune response → CMI key to control the infection

T_H1 cells → IF-γ → MP activation → ↑ killing

Clinical manifestations

* Clasical triad → Profuse night sweats + arthralgia/ arthritis + hepatosplenomegaly
  - Foul smelling perspiration : clasical sign
    sweating

* Typhoid like illness → Resembles typhoid except less acute, less severe more musculoskeletal systems

* Undulating fever → b/w febrile periods there will be afebrile periods
  - Also called malta fever

* Musculoskeletal symptoms : Mimic skeletal TB
  - Vertebral osteomyelitis
  - Septic arthritis

* Other non-specific symptoms : Abdominal pain, headache, diarrhea, rash, weakness

* CNS : Depression, lethargy

* CVS - Endocarditis

* Genitourinary manifestations

Laboratory diagnosis

- Specimens - Blood, BM, CSF
- Blood cultures by
  → Castaneda's biphasic media (BHI broth/ agar)
  → Automated techniques such as BACTEC or BACT/ALERT

full C B

→ Culture conditions : Obligate aerobes, but growth promoted in presence of 5-10% of CO_2.

- CULTURE SMEAR & MOTILITY TESTING

→ Non motile gram negative coccobacilli

- IDENTIFICATION

By automated identification systems - MALDI-TOF or VITEK

or by conventional biochemical tests
↳ Catalase & oxidase +

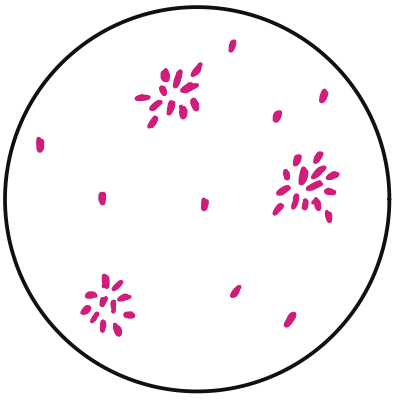
- SEROLOGICAL TESTS (AB detection)

- Standard agglutination test (SAT) - detects IgM (Tube agglutination test / Cauta agglutination)

- Tests to detect IgG AB - 2mE test, ELISA
(mercaptoethanol (mE))

- MOLECULAR METHODS

PCR detecting nrs-nrl gene, Omp2 gene, protein BCSP31 & IS711 insertion sequence



Wayne - Y
doxy
Gentamicin

Treatment

Standard regimen : Gentamicin (2 days) + doxycycline (6w)

LONG regimen : Rifampin (6w) + doxycycline (6w)

CNS involvement : Ceftriaxone

LEPTOSPIROSIS / Weil's disease

Laboratory diagnosis

Specimens : CSF & blood (first 10 days) & urine (2/w 10-30 days)

I Microscopy

Leptospira (spirochete) is very thin ∴ cannot be seen under light microscope

- Dark ground or phase contrast microscope or silver impregnation staining (syphilis) ⇒ spirally coiled bacilli (tightly & regularly coiled), with characteristic hooked ends like umbrella handle

II Isolation

medium : EMJH medium , Korthof's & Fletcher's media
(every mb just hates) (Forth off aan)

III Serology for Ab detection

- Genus specific tests : ELISA - detects IgM & IgG , lepto dipstick assay - IgM only
  Immunochromatographic (ICT) - both IgG & IgM
- Serovar specific test : microscopic agglutination test → Gold standard

Molecular methods

- PCR

Non-specific findings : Altered renal & liver function test

Etiological agents : L. interogans & L. biflexa — Leptospira ?

Mode of transmission : Zoonotic – Brucellosis also

Risk factors : Lower socioeconomic status
Urban & rural areas
Rainfall & floods

3R's : Rodents, rainfall, rice field

Pathogenesis :

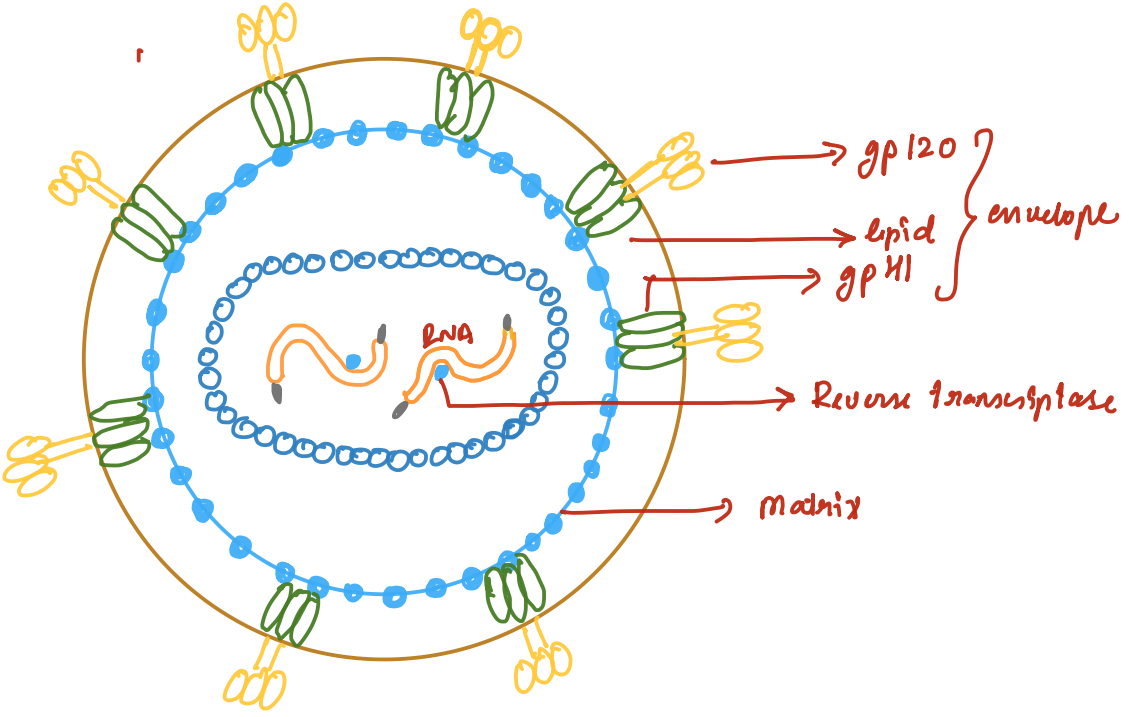
- 1st phase (septicemia phase) – hematogenously → vascular damage → revolution & invasion of tissues
- 2nd phase (immune phase) – Ab develop, spirochete disappears from blood. Ag-Ab deposited in various organs.

Clinical manifestations :

- Mild anicteric febrile illness - flu like illness
- Weil's disease : Hepato-renal - hemorrhagic syndrome

HIV/AIDS

Morphology



Nucleocapsid : Isosahedral in symmetry

RNA → 2 identical copies

Enzymes → RT, integrase, proteases

HIV genes : gag, pol, env & 6 non-structural genes

- env → codes for envelope gp 120 & 41
- pol → codes for viral enzymes
- gag → p18, p24 & p15 (codes for core & shell)

Opportunistic infections

BACTERIAL : Extrapulmonary TB, recurrent septicemia, disseminated non-TB mycobacterial infection

VIRAL : CMV, chronic HSV infection, multifocal leukoencephalopathy

FUNGAL : esophageal candidiasis, disseminated mycoses, pneumocystis jiroveci pneumonia

Laboratory diagnosis — 3 C's : Consent, Confidentiality, Counselling

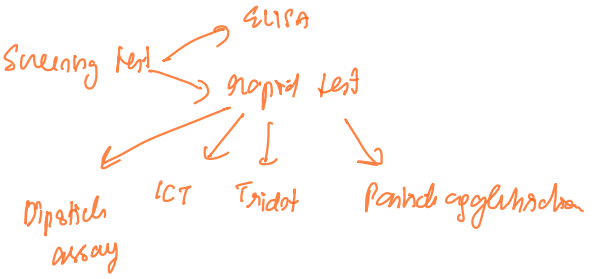
1) Screening tests

- Detects AB against HIV

Screening tests :

- less time
- High sensitivity & specificity
- Should be confirmed

Screening } AB detection
Supplement }



ELISA

- Easy, large no. of samples, sensitive, specific, cost effective
- 2 types : 3rd generation & 2nd generation

RAPID TEST — ICT, Tridot test, Particle agglutination tests, dipstick assay

- less than 30 min
- Do not req. special equipment

Rapid test : card tests

2) Supplemental tests

- Highly specific AB detection

to confirm the true result of screening test

- Used for validation of +ve results of screening tests
- Expensive, Labor intensive.

Supplemental → Western blot
Supplemental → line immuno assay (LIA)

→ WESTERN BLOT

Principle : Immunoblot technique

- Detects individual AB against gag, pol, env gene & its products
- Appears as distinct bands on nitrocellulose strip

→ LINE IMMUNO ASSAY (LIA)

3) Confirmatory tests

- Detection of p24 core Ag

- Becomes detectable after 12-26 days & last for 3-4 weeks

- Elevated during advance stages

Uses :
- Confirmation of HIV/AIDS
- Diagnosis of HIV during "window period"
- " of HIV in infants
- Monitoring treatment progress

* Viral RNA detection

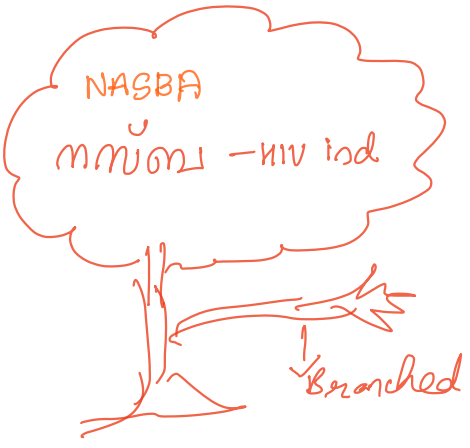
- gold standard
- detected 10-14 days after infection

↳ Reverse transcriptase RT-PCR

→ Branched DNA assay

→ NASBA (nucleic a sequence - based amplifications)

→ real time RT-PCR



Uses :
- most sensitive & specific - BEST METHOD FOR CONFIRMATION
- during window period
- can quantify the viral load
- Differentiate b/w HIV 1 & HIV 2
- Detection of drug resistance genes.

- Viral DNA detection : diagnosis of pediatric HIV

3) NON SPECIFIC IMMUNOLOGICAL METHODS

- Low CD4 T cell count
- Hypergammaglobulinemia
- Altered CD4 : CD8 ratio

Diagnosis of HIV in window period

Window period - initial time interval b/w exposure & appearance of detectable level of AB in serum

↳ AB appear in blood within 2-8 weeks after I, but becomes detectable after 3-12 weeks with assays.

22 days → 3rd generation AB detection kits

p24 Ag detection - by 4th gen ELISA : detected after 12-26 days after infection

HIV RNA detection (by RT-PCR) : Best method

↳ detects around 10-14 days after infection

DENGUE

- m/c arbovirus found in India
- family Flaviviridae
- contains ssRNA
- Vector : *Aedes aegypti* - principle vector

arbovirus
- Togaviridae
- Flaviviridae
- Bunyaviridae
- Rhoviridae
- Rhabdoviridae

Egypti (♀) Dengue (♂)

Pathogenesis

1° dengue infection : 1st time infected with any one serotype

2° dengue infection : more severe - infection with another 2nd serotype

1997 WHO classification

1) Dengue fever
2) Dengue haemorrhagic fever
3) Dengue shock syndrome

2009 WHO classification

(1) Dengue with/without warning signs
(2) Severe dengue

Probable dengue

Fever & 2 of the following
- Nausea, vomiting
- Rash
- Aches & pains
- Leukopenia
- Any warning signs

warning signs

- Abdominal pain
- Persistent vomiting
- mucosal bleed
- Lethargy, restlessness
- ↓ in platelets
- Liver enlargment

• Severe plasma leakage
- shock
- fluid accumulation

• Severe bleeding

• Severe organ involvement

Laboratory diagnosis

NS1 - Dengue
ELISA, ICT

- NS1 Ag detection
  - ↳ ELISA & ICT
  - NS1 Ag becomes detectable from day 1
  - Highly specific

- AB detection
  - * In 1° infection → AB response slow & low titers
    IgM appears after 5 days of fever
    ↳ Acute
  - * In 2° infection → IgG AB titer rise rapidly
  - * In past infection → IgGs remain detectable for over 60 yrs
  - * MAC - ELISA (IgM - AB capture ELISA) — MAC captures IgM ABs by using anti-IgM ABs
  - * Neutralization tests : Plaque reduction test, microneutralization test

* Rapid diagnostic test available (e.g. ICT) - for IgM AB

- Virus isolation
  - Detected in blood from -1 to +5 days
  - Done by inoculation into mosquito cell line (C6/36 & AP 61) or in mouse

- Molecular method
  - Detection of specific gene of viral RNA by RT-PCR

Treatment :

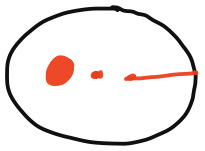
No specific antiviral therapy.

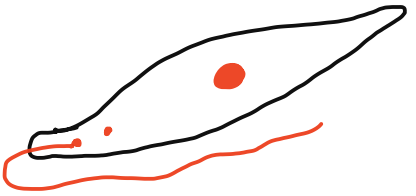
- Replacement of plasma losses
- Correction of electrolyte
- Platelet transfusion

LEISHMANIAS

Etiological agent : flagellated protozoa of the genus leishmania, which are obligatory intracellular protozoa

morphological forms : Amastigote & Promastigote





- L. donovani
- L. infantum
- L. chagasi

Vector : female sandfly vector

Clinical forms :

- Visceral leishmaniasis / Kala azhar : Affects viscera (spleen, liver, BM etc)

Visceral leishmaniasis / Kala azhar

↳ L. donovani & L. infantum

life cycle :

L. donovani completes its life cycle in 2 hosts → man & sandfly (F)

↳ Phlebotomus argentipus

- Infective form → Promastigote - alimentary canal of F. sandfly
- Mode of transmission → Bite → into skin of the man
- In humans : Promastigote → amastigote as they are phagocytosed by skin macrophages
  - Amastigote multiplies in the MP ⇒ cell ruptures → release into circulation

- Amastigote to various organs & invade reticuloendothelial cells

- In Sandfly : During blood meal, amastigotes → promastigotes in the insect gut.

Clinical features :

Hallmark of VL → Pentad [fever, weight loss, hepatosplenomegaly, pancytopenia, hypergammaglobulinemia]

fever, splenomegaly, hepatomegaly, lymphadenopathy, hyperpigmentation, pedal edema, Hematological abnormalities

Laboratory diagnosis

- microscopy
  - Giemsa staining, detects LD bodies (RP with amastigotes)

  Samples include :

  * Splenic aspiration - most sensitive
  * BM aspiration & MJC specimen
  * lymph node aspiration
  * liver biopsy
  * Peripheral BC - HIV infected

- CULTURE

  detects promastigotes - useful for species identification & drug sensitivity testing

  → NNN medium

  → Schneider's liquid medium

- AB DETECTION
  - ELISA, IFA, direct agglutination
  - ICT using rK39 Ag

- Ag DETECTION
  - carbohydrate Ag in urine (Latex AT)

- MOLECULAR METHOD
  - PCR, Nt-PCR

- Leishmanin test (montenegro test)
  - indicates good CMI

- NON SPECIFIC TEST
  - Hypergammaglobulinemia
  - Pancytopenia

Weil-Felix test — Richettsial infections

Principle: Tube agglutination test

- Antigenic cross reactivity

↳ Alkali stable LPS Ag of rickettsia 𝕀𝕘 to strains of Proteus (OX19, OX2 & OXK)

∴ Richettsial AB detected by using proteus Ag.

Procedure: Serial dilutions of patient's serum + Proteus strains (OX19, OX2, OXK)

Result: After 5-7 days of onset of fever.

1:160 titre — possible infection

False +ve: For proteus infections

False -ve: due to excess AB's in patient's serum

WF test: Non-specific test

Specific test → Indirect Immunofluorescence test.

Lyme disease

Borrelia burgdorferi — tick bite — BSK medium

if ELISA +ve → western blot

Doxycycline

Pathogenesis of HIV

Attachment
gp120 + CD4 receptor (on host cell surface) [coreceptors eg. chemokine receptors, needed to gain entry (CXCR4, CCR5)]

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Fusion - for fusion with host cell - GP41 needed

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After fusion, HIV nucleocapsid enters cytoplasm

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uncoating & release of

2 copies of ssRNA & enzymes (RT & integrase)

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1 ssRNA $\xrightarrow{RT}$ ssDNA

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DNA - RNA hybrid

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RNA degraded by viral endonuclease

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ssDNA $\xrightarrow[RT \rightarrow \text{DNA polymerase}]{\text{replicates}}$ dsDNA

↓

transported to host cell nucleus

↓

viral dsDNA integrates into chromosome

mediated integrase enzyme

(integrated virus is called provirus)

- In this integrated state, HIV establishes a latency for variable period but it can replicate even in latent state & is infectious.