Dengue: The Disease

- Infection of tropical and subtropical regions
- Nonspecific febrile illness to fatal hemorrhagic disease
- Infection caused by a virus and spread by an insect vector – the mosquito

Dengue : The virus

- Flavi viruses: RNA
- Arbovirus group
- 4 serotypes – Den 1- 4
- Cycle involves humans and mosquitos
- Infection with one virus gives immunity to that serotype only

Dengue: The vector

- Aedes egyptii, A albopictus less commonly
- Domestic day biting mosquito
- Prefers to feed on humans
- Breeds in stored water
- Short flight range
- May bite several people in same household

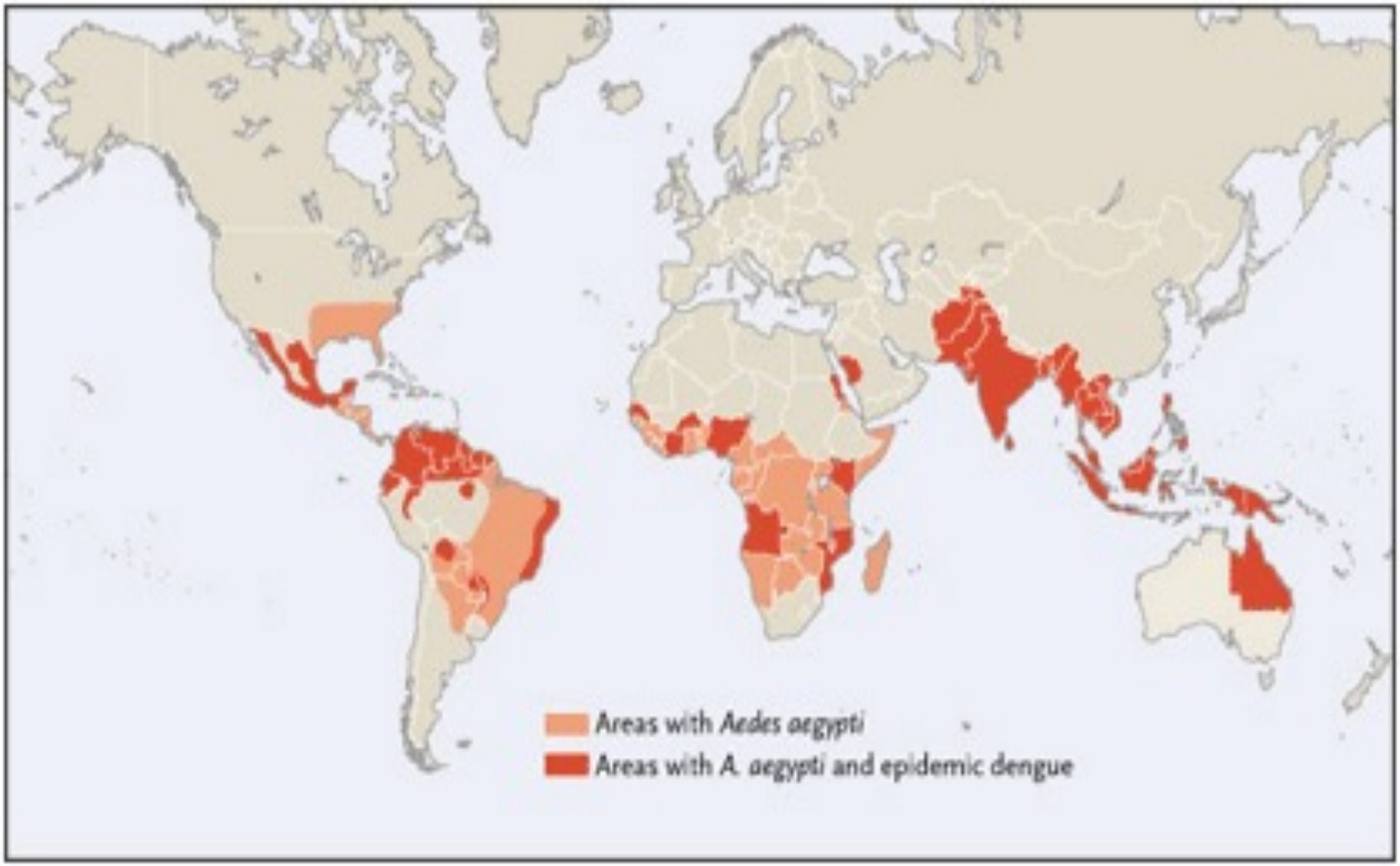
Dengue: History

- First reported epidemics in 1779 –80 in Asia, Africa and North America.
- Considered a mild non fatal disease
- Epidemics every 10-40 years due to introduction of new serotype
- After World War II, pandemic of dengue which began in Southeast Asia, expanded geographical distribution, epidemics with multiple serotypes and emergence of DHF

Dengue: A re-emerging infection

- 1980s: a second re-expansion of DHF in Asia with epidemics in India, Sri Lanka and Maldives, Taiwan, PRC; Africa and Americas

- Progressively larger epidemics
- Primarily urban


Areas with *Aedes aegypti*
Areas with *A. aegypti* and epidemic dengue

Reasons for resurgence

- Uncontrolled urbanisation and population growth → substandard housing, inadequate water, sewer and waste management
- Deterioration of public health infrastructure
- Faster travel
- Ineffective mosquito control in endemic regions
- Hyperendemicity: prevalence of multiple serotypes

Dengue in India

- First isolated in Calcutta in 1945
- Extensive epidemics since 1963
- DHF, DSS epidemics over last 4 decades
- Severe epidemic in Delhi in 1996, 2006; Lucknow 1998, 2003, 2006
- All 4 serotypes are prevalent
- Viruses prevalent all over except Himalayan region & Kashmir

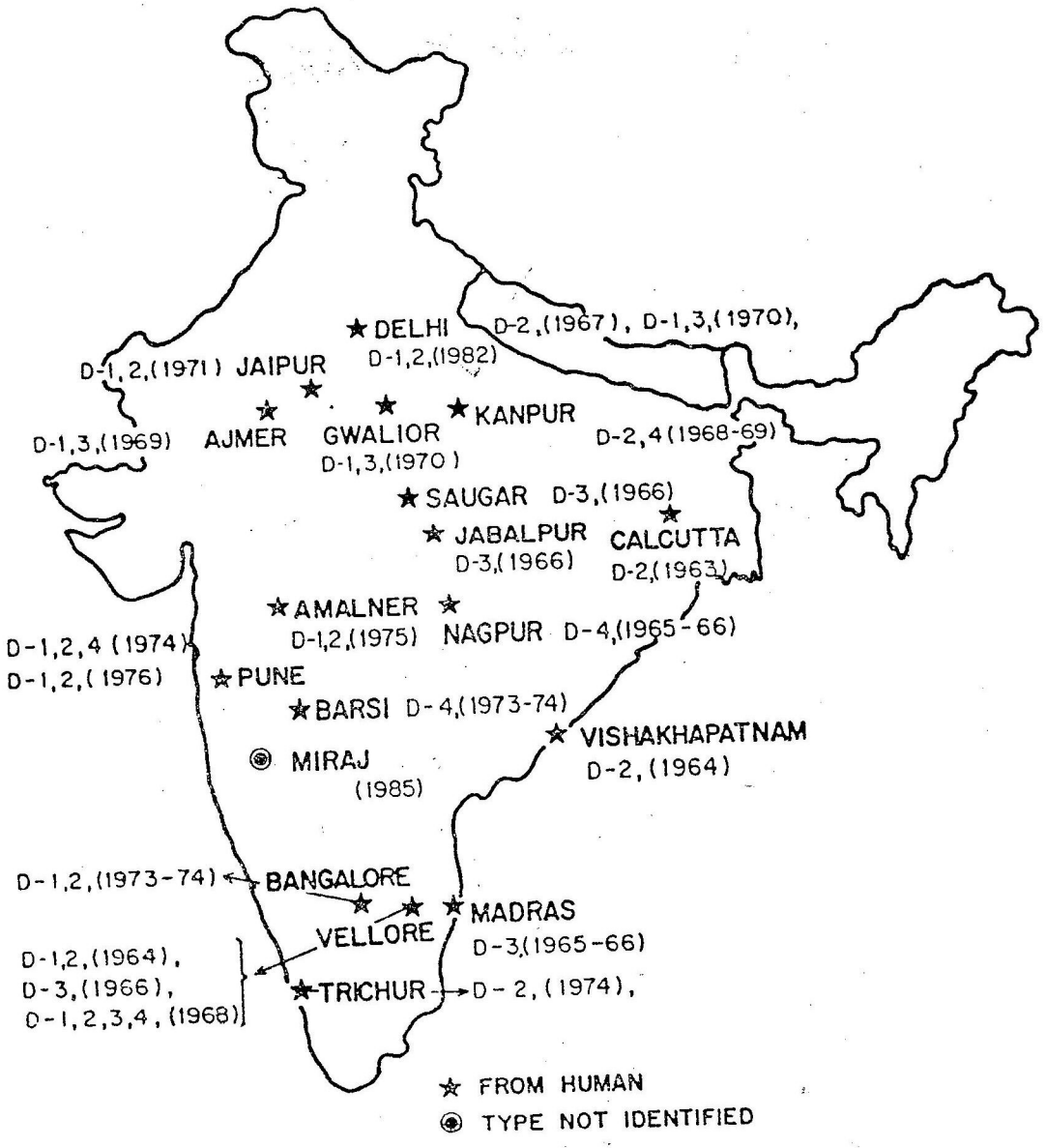


Fig. Epidemics of dengue fever in India

Dengue Fever : Clinical Features

- Incubation period 2-7 days
- Sudden fever 40-41 C
- Nonspecific constitutional symptoms
- Severe muscle aches, retro-orbital pain
- Hepatomegaly
- Rash
- Facial flush
- Fever subsides in 2-7 days, may be biphasic

DDx

- Respiratory Infections
- Measles
- Rubella (German measles)
- Malaria
- Meningoencephalitis
- Pyelonephritis
- Septicemia

WHO case definition for DF:

Acute Febrile illness with 2 or > of the following:

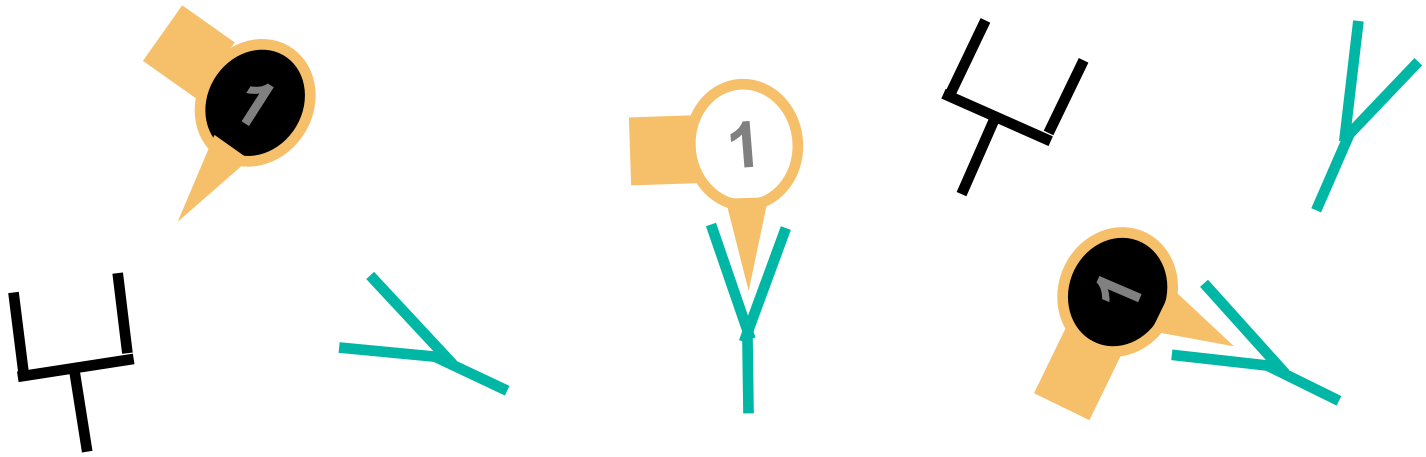
- Headache
- Retro-orbital pain
- Myalgia
- Arthralgia
- Rash
- Hemorrhagic manifestations
- Leukopenia

Hepatomegaly common

DHF: Pathogenesis

- Secondary infection with another serotype leads to 'antibody mediated enhancement'
- Heterotypic antibodies are non protective and fail to neutralise the virus
- Virus-antibody complexes taken up by monocytes
- Virion multiplication in human monocytes is promoted
- Activation of CD4+ and CD8+ lymphocytes → release of cytokines
- Complement system activated with depression of C3 & C5

Homologous Antibodies Form Non-infectious Complexes



1 Dengue 1 virus

Neutralizing antibody to Dengue 1 virus

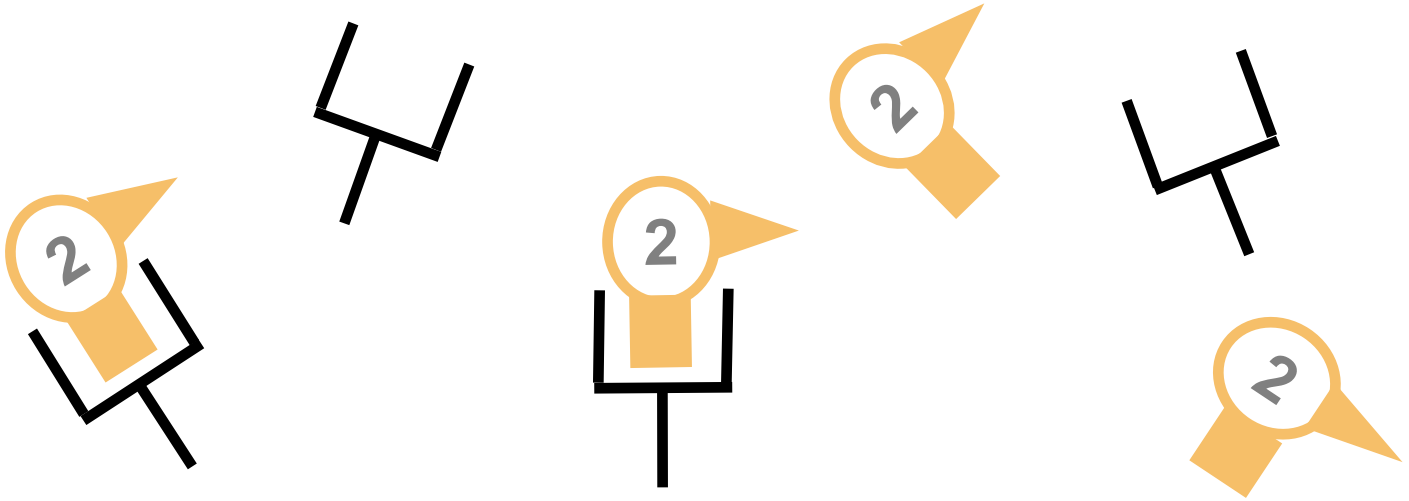
Non-neutralizing antibody

1 Complex formed by neutralizing antibody and virus

Hypothesis on Pathogenesis of DHF (Part 2)

- In a subsequent infection, the pre-existing heterologous antibodies form complexes with the new infecting virus serotype, but do not neutralize the new virus

Heterologous Antibodies Form Infectious Complexes



2 Dengue 2 virus

Non-neutralizing antibody to Dengue 1 virus

2 Complex formed by non-neutralizing antibody and virus

Hypothesis on Pathogenesis of DHF (Part 3)

- **Antibody-dependent enhancement** is the process in which certain strains of dengue virus, complexed with non-neutralizing antibodies, can enter a greater proportion of cells of the mononuclear lineage, thus increasing virus production

DHF: Pathophysiology

- Activation of complement → Increased vascular permeability →loss of plasma from vascular compartment → hemoconcentration & shock
- Disorder of haemostasis involving thrombocytopenia, vascular changes and coagulopathy
- Severe DHF with features of shock : DSS

DHF: WHO Criteria for diagnosis

Often occurs with defervescence of fever, swelling

All of the following must be present:

- **Fever**
- **Hemorrhagic tendencies:**
  - +ve tourniquet test
  - Petichiae, ecchymosis or purpura
  - Bleeding from other sites
- **Thrombocytopenia (<=100,000/cu mm)**
- **Evidence of plasma leak**
  - Rise in hematocrit > 20% above average
  - Drop in Hct
  - Pleural effusion/ascites/hypoproteinemia

DSS: WHO Criteria for diagnosis

All of the above + evidence of circulatory failure:

- Rapid, weak pulse
- Narrow pulse pressure < =20 mm hg
- Cold clammy skin
- Restlessness

Often present with abdominal pain; mistaken for acute abdominal emergency

Grading of DV infection

DF/DHF	Grade	Symptoms	Lab
DF		**Fever with 2 or > of: headache/retro-orbital pain, myalgia, arthralgia**	**Leukopenia, occasionally thrombocytopenia, no evidence of plasma leak**
DHF	**I**	**Above + +ve tourniquet test**	**Platelets < 100,000, Hct rise > 20%**
DHF	**II**	**Above + spontaneous bleeding**	**,,**
DHF	**III/DSS**	**Above + s/o circulatory failure**	**,,**
DHF	**IV/DSS**	**Profound shock with undetectable BP and pulse**	**,,**
			Lab evidence of Dv infection

Immune response to Dengue infections

- Primary Infection: IgM antibody in late acute/ convalescent stage; later IgG which lasts for several decades
- Secondary infection: High IgG level, small rise in IgM
- Cross reactions with other flaviviruses
- Infection with one serotype does not protect against other serotypes

Lab Diagnosis of Dengue infection:

- Dengue HI test in paired sera showing 4 fold rise or fall: cross reactivity
- IgM type antibodies in late acute/convalescent sera in primary infection
- IgG type antibodies in high titre in secondary infection
- Viral isolation: sensitivity < 50%
- RT- PCR: sensitivity > 90%

WHO Lab Criteria for Dengue infection:

Probable Case:

- CF + Supportive Serology: Acute HI titre > 1280, comparable IgG ELISA or +ve IgM
- or occurrence at same location & time as other confirmed cases

Confirmed case:

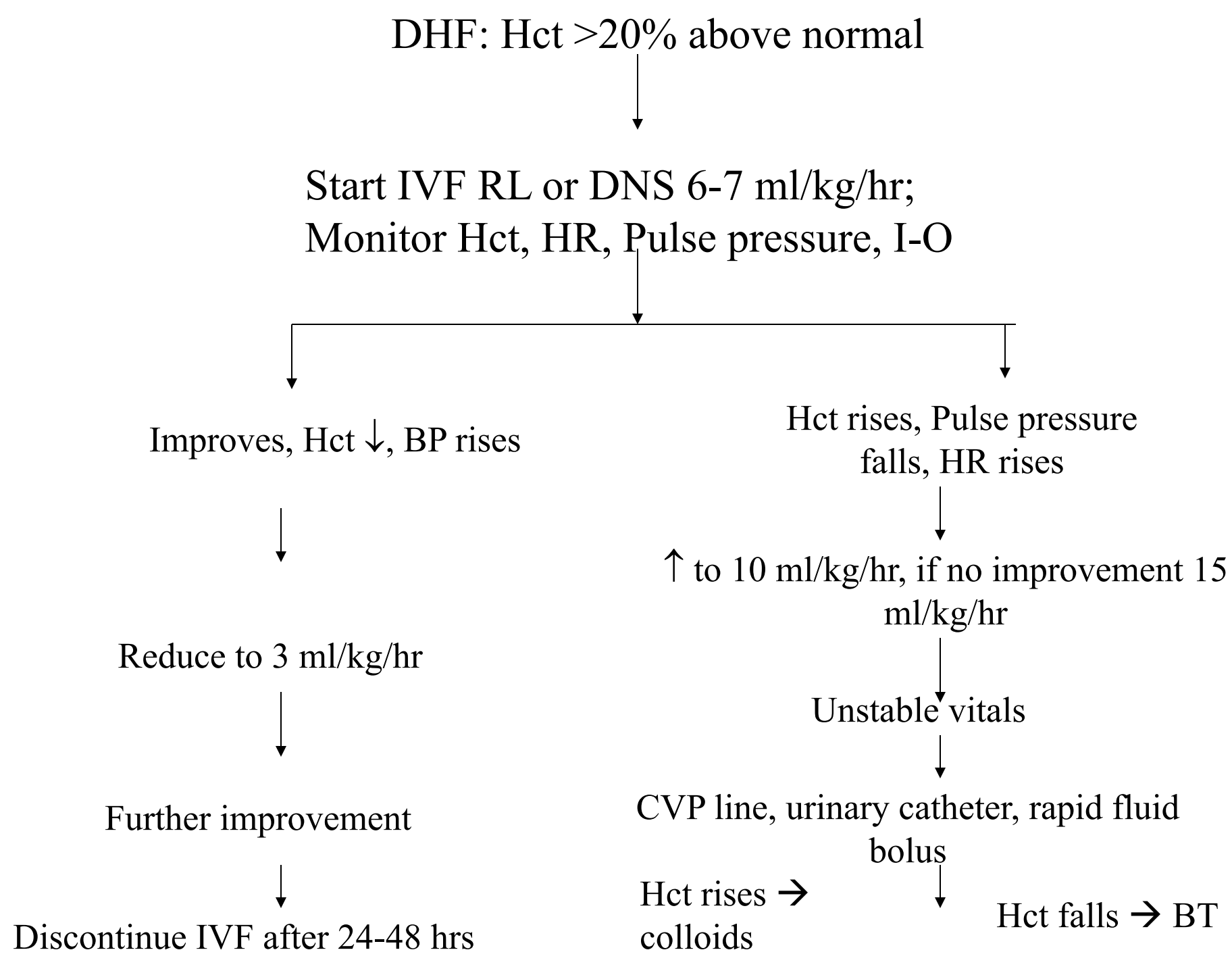
- isolation of virus from serum/ autopsy specimen
- Demonstration of dengue virus antigen in serum/ CSF/ Autopsy tissue
- Detection of dengue virus genome by PCR

Management: DF

- No specific Tt
- Analgesics/antipyretics
- Avoid agents which may impair platelet function eg aspirin

Management: DHF:

- Hospitalise
- Closely monitor for shock; repeated hematocrit measurements
- If Hct rising by >20%, IV fluids as 5% deficit
- Start with DNS 6-7 ml/kg/hr.
- Improves → reduce gradually over 24-48 hrs
- No improvement → ↑ upto 15 ml/kg/hr → colloid solution


DHF: Hct >20% above normal
Start IVF RL or DNS 6-7 ml/kg/hr;
Monitor Hct, HR, Pulse pressure, I-O
Improves, Hct ↓, BP rises
Reduce to 3 ml/kg/hr
Further improvement
Discontinue IVF after 24-48 hrs
Hct rises, Pulse pressure falls, HR rises
↑ to 10 ml/kg/hr, if no improvement 15 ml/kg/hr
Unstable vitals
CVP line, urinary catheter, rapid fluid bolus
Hct rises → colloids
Hct falls → BT

Revised WHO classification (2009)

Probable dengue	Warning signs	Severe dengue
Live in/travel to endemic area	Abdominal pain or tenderness	Severe plasma leak
Fever + 2 of :	Persistent vomiting	Shock
Nausea, vomiting	Clinical fluid accumulation	Fluid accumulation with respiratory distress
Rash	Lethargy/ restlessness	Severe bleeding
Aches & pains	Liver enlargement > 2 cm	Severe organ involvement
Tourniquet test +ve	Laboratory increase in HCT concurrent with rapid decrease in platelet count	Liver ALT or AST >=1000
Leucopenia		Impaired consciousness
Any warning sign		Heart or other organs

Prevention

- **Antimosquito measures**
  - Avoid open stagnant water in and around home
  - Bed nets
  - Long sleeved clothing
  - In house spraying
  - repellants

- **Pediatric dengue vaccine**

THANK YOU