CLINICAL PROFILE AND OUTCOME OF DENGUE FEVER AMONG CHILDREN ADMITTED AT TIRUNELVELI MEDICAL COLLEGE HOSPITAL

Dissertation submitted to

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In partial fulfillment of the regulations
for the award of the degree of

M.D. BRANCH – VII

PEDIATRICS

TIRUNELVELLI MEDICAL COLLEGE & HOSPITAL,

THE TAMILNADU DR.M.G.R. MEDICAL UNIVERSITY,

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APRIL 2012

CERTIFICATE

This is to certify that the dissertation entitled "**CLINICAL PROFILE AND OUTCOME OF DENGUE FEVER AMONG CHILDREN ADMITTED AT TVMCH"** is the bonafide work of **Dr.R.Karthikeyan** in partial fulfillment of the requirements for the degree of **Doctor of Medicine in Paediatrics** Examination of the Tamilnadu Dr.M.G.R. Medical University to be held in April 2012.

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DECLARATION

I, **Dr.R.ARTHIKEYAN**, solemnly declare that dissertation titled, "**CLINICAL PROFILE AND OUTCOME OF DENGUE FEVER AMONG CHILDREN IN TVMCH**" is a bonafide work done by me at The Department of Paediatrics, Tirunelvelli Medical College & Hospital during 2009 – 2012 under the guidance and supervision of **Dr.T.KATHIR SUBRAMANIUM M.D., D.C.H.,** and **Dr.S.DEVIKALA M.D., D.C.H.,** Professors, TIRUNELVELLI MEDICAL COLLEGE The Dissertation is submitted to **The Tamilnadu Dr.M.G.R. Medical University**, towards partial 3ulfilment of requirement for the award of **M.D. Degree (Branch – VII) in Paediatrics.**

Place :

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CONTENTS

INTRODUCTION

Dengue viral infection is the most common mosquito borne disease in the world with varied presentations, high morbidity and high mortality patterns. 2.5 billion people – two fifths of the world's population in tropical and subtropical countries are at risk [1]. An estimated 50 million dengue infections occur worldwide annually. A very large proportion (approximately 90%) of them are children aged less than five years, and about 2.5% of those affected die. Epidemics of dengue are increasing in frequency. During epidemics, infection rates among those who have not been previously exposed to the virus are often 40% to 50% but can also reach 80% to 90%. *Aedes (Stegomyia) aegypti* is the primary epidemic vector.

Primarily an urban disease, dengue and DHF are now spreading to rural areas worldwide. Dengue viral infections classified on the basis of WHO criteria[2] as follows:

1. Dengue fever (DF): Dengue seropositive without bleed.
2. Dengue fever with unusual bleed (DFB): Dengue seropositive with bleeding tendencies, not satisfying WHO criteria for DHF.
3. Dengue hemorrhagic fever (DHF): Dengue seropositive with bleeds with evidence of plasma leakage.
4. Dengue shock syndrome (DSS): DHF with evidence of peripheral circulatory failure.

Dengue generally an acute febrile illness, and sometimes biphasic fever with severe headache, myalgia, arthralgia, rashes, leucopenia and thrombocytopenia may also be observed. DHF is characterized by the acute onset of high fever and is associated with signs and symptoms similar to DF in the early febrile phase. There are common haemorrhagic manifestation such as positive tourniquet test (TT), petechiae, easy bruising and/or GI haemorrhage in severe cases. By the end of the febrile phase, there is a tendency to develop hypovolemic shock (dengue shock syndrome) due to plasma leakage. The presence of preceding warning signs such as persistent vomiting, abdominal pain, lethargy or restlessness, or irritability and oliguria are important for intervention to prevent shock.

Abnormal haemostasis and plasma leakage are the main patho-physiological hallmarks of DHF. Thrombocytopenia and rising haematocrit/ haemoconcentration are constant findings before the subsidence of fever/ onset of shock. DHF occurs most commonly in children with secondary dengue infection. It has also been documented in primary infections with DENV-1 and DENV-3 as well as in infants.We live in a country with resource limited settings confounded by public ignorance about the disease and poor access to health care. Severity is high in paediatric age group.

No vaccine is available for preventing this disease at present. Chandrakanta et al[3] describe the varied manifestations of dengue viral infection

as seen in hospitalized children in northern India. Manjunath J. Kulkarni et al[4] in their study describe various clinical manifestations.

The demographic pattern and the trend of illness are vastly changing every year through the past decade. South India and especially South Tamilnadu has witnessed several dengue epidemic outbreaks during the past few years. Early recognition and prompt initiation of appropriate management is vital. Additional studies about the disease can lead to change in guidelines and alterations in public health programs. Here, I have made an attempt to study the clinical profile and outcome of dengue viral infection the time period from Dec 2009 to Dec 2010.

OBJECTIVE

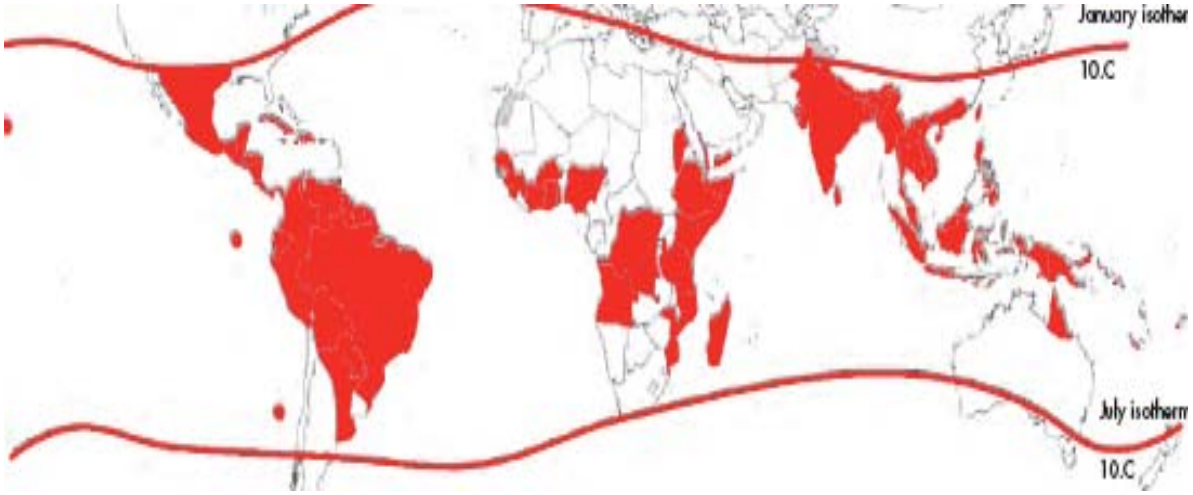
To study the clinical profile and outcome of dengue fever in children.

LITERATURE REVIEW

EPIDEMIOLOGY:

Dengue is the most rapidly spreading mosquito-borne viral disease in the world. Dengue is an example of a disease that may constitute a public health emergency of international concern with implications for health security due to disruption and rapid epidemic spread beyond national borders[5]. The global prevalence of dengue has grown dramatically in the last decade, with increasing geographic expansion to new countries AND, from urban to rural settings. The disease is now endemic in more than 100 countries in africa, the americas, the eastern mediterranean, southeast asia, and the western pacific, threatening more than 2.5 billion people[6].Dengue is believed to infect 50 to 100 million people worldwide a year with half a million life-threatening infections requiring hospitalization, resulting in approximately 12,500 to 25,000 deaths. Over the past three decades, there has been a dramatic global increase in the frequency of dengue fever, and its severe forms- DHF and DSS and their epidemics .

There is no specific treatment for dengue, but appropriate medical care frequently saves the lives of patients with the more serious dengue haemorrhagic fever. The most effective way to prevent dengue virus transmission is to combat the disease-carrying mosquito[1]



The first confirmed epidemic of DHF was recorded in the Philippines in 1953–1954 and in Thailand in 1958. Since then, several Member countries of the WHO have been reporting outbreaks.

South-East Asia Region

Of the 2.5 billion people around the world living in dengue endemic countries and at risk of contracting DF/DHF, 1.3 billion live in 10 countries of the WHO South-East Asia (SEA) Region which are dengue endemic areas. . Epidemic dengue is a major public health problem in most of these countries.By 2009, all Member countries except the Democratic People's Republic (DPR) of Korea reported dengue outbreaks. Reported case fatality rates for the region are approximately 1%, but in India, Indonesia and Myanmar, focal outbreaks away from the urban areas have reported case-fatality rates of 3--5%. The countries of the region have been divided into three distinct categories with different dengue transmission potential

INDIA falls under **Category A which** includes countries where dengue is a

 Major public health problem.

 Leading cause of hospitalization and death among children.

 Hyperendemicity with “all four serotypes” circulating in urban areas.

 Spreading to rural areas.

Cyclic epidemics are increasing in frequency and in-country geographic expansion is occurring in India.

Dengue prevention and control will be implemented through the Bi-regional Dengue Strategy (2008--2015) of the WHO South-East Asia and Western Pacific regions[7]

The virus

The dengue viruses are members of the genus *Flavivirus* and family *Flaviviridae*. These small (50nm) viruses contain single-strand RNA as genome. The virion consists of a nucleocapsid with cubic symmetry enclosed in a lipoprotein envelope. The dengue virus genome is 11,644 nucleotides in length, and is composed of three structural protein genes encoding the nucleocaprid or core protein (C), a membrane-associated protein (M), an envelope protein (E), and seven non-structural protein (NS) genes. Among nonstructural proteins, envelope glycoprotein, NS1, is of diagnostic and pathological importance. It is 45 kDa in size and associated with viral haemagglutination and neutralization activity.[8]

The dengue viruses form a distinct complex within the genus *Flavivirus* based on antigenic and biological characteristics. There are four virus serotypes,

which are designated as DENV-1, DENV-2,DENV-3 and DENV-4. Infection with any one serotype confers lifelong immunity to that virus serotype.Although all four serotypes are antigenically similar, they are different enough to elicit cross-protection for only a few months after infection by any one of them. Secondary infection with another serotype or multiple infections with different serotypes leads to severe form of dengue (DHF/DSS).

There exists considerable genetic variation within each serotype in the form of phylogenetically distinct "sub-types" or "genotypes". Currently, three sub-types can be identified for DENV-1, six for DENV-2 (one of which is found in non-human primates), four for DENV-3 and four for DEN-4, with another DENV-4 being exclusive to non-human primates. Dengue viruses of all four serotypes have been associated with epidemics of dengue fever (with or without DHF) with a varying degree of severity.Among them, "Asian" genotypes of DEN-2 and DEN-3 are frequently associated with severe disease accompanying secondary dengue infections Intra-host viral diversity (quasispecies) has also been described in human[9]

Plasma levels of secreted NS1 (sNS1) correlate with viral titers, being higher in patients with DHF compared with dengue fever[10] . Moreover, elevated free sNS1 levels within 72 hours of onset of illness identify patients at risk of developing DHF. Very high levels of NS1 protein are detected in acute phase samples from patients with secondary dengue infections but not primary infections. This suggests that NS1 may contribute to formation of circulating

immune complexes, which are thought to have an important role in the pathogenesis of severe dengue infections[11] .The dengue virus shares antigenic epitopes with other flaviviruses such as Japanese encephalitis virus. These shared epitopes may lead to production of cross reactive antibodies and hence interfere with serological diagnosis. However,antibodies directed to the prM protein of dengue viruses are species specific (not cross reactive with those of other flaviviruses) and may be useful for seroepidemiological studies in dengue (especially in countries where other flaviviruses are endemic)

Vectors of dengue

Aedes (Stegomyia) aegypti (*Ae. aegypti)* and *Aedes (Stegomyia) albopictus* (*Ae. albopictus)* are the two most important vectors of dengue

Aedes (Stegomyia) aegypti

Aedes aegypti is a container breeding, day biting mosquito found in tropical and subtropical areas[12]. The immature stages are found in water-filled

habitats, mostly in artificial containers closely associated with human dwellings and often indoors. This maximizes man-vector contact and minimizes contact with insecticides sprayed outdoors, hence contributing to difficulty in controlling this vector[13]. Studies suggest that most female *Ae. aegypti* may spend their lifetime in or around the houses where they emerge as adults. This means that people, rather than mosquitoes, rapidly move the virus within and between communities . Increased transport, human contact, urbanization and the proliferation of drinking water supply schemes in rural areas ultimately led to the species getting entrenched in both urban and rural areas . On account of the species' high degree of domestication and strong affinity for human blood, it achieved high vectorial capacity for transmission of DF/DHF.Significant increases in the mosquito larval populations are seen during the rainy season. This may be a reason why epidemics of dengue tend to coincide with the rainy season[10].Furthermore,ambient temperature and relative humidity affect viral propagation in mosquitoes; rates being highest in climates resembling the rainy season[10].

After biting an infected human, dengue viruses enter an adult female mosquito. The virus first replicates in the midgut, reaches the haemocoel and haemolymph, and then gains access to different tissues of the insect. After viral replication in the salivary glands, the infected mosquito can transmit the virus to another human[11] . Compared with uninfected mosquitoes, infected ones take

longer to complete a blood meal. This may contribute to the efficiency of A .aegypti as a dengue viral vector.

Aedes (Stegomyia) albopictus belongs to the *scutellaris* group of subgenus *Stegomyia*. It is a predominant Asian species. Dengue outbreaks have also been attributed to *Aedes albopictus*, *Aedes polynesiensis* and several species of the *Aedes scutellaris* complex. Each of these species has a particular ecology, behaviour and geographical distribution.

Clinical manifestations

Dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome[14].Dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations[15] . Dengue virus infection may be asymptomatic or may cause undifferentiated febrile illness (viral syndrome), dengue fever (DF), or dengue haemorrhagic fever (DHF) including dengue shock syndrome(DSS)

Undifferentiated fever

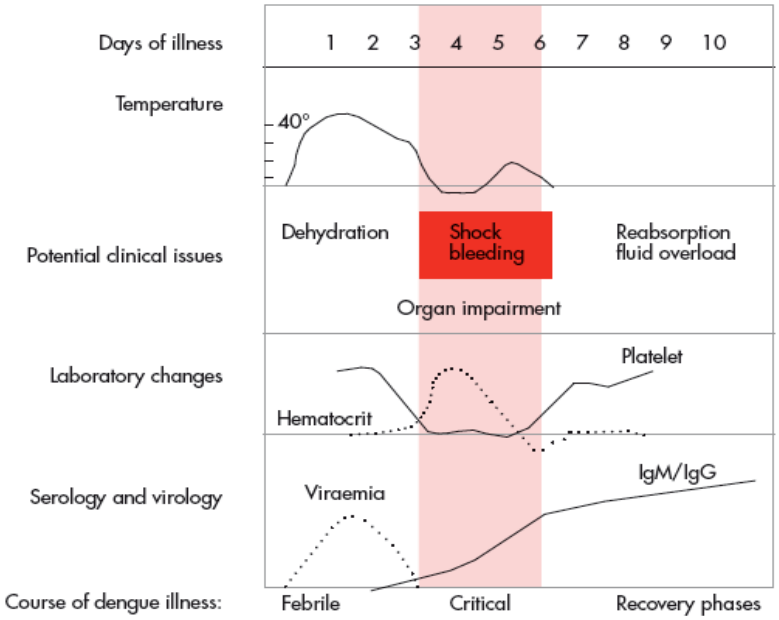
Infants, children and adults who have been infected with dengue virus, especially for the first time (i.e. primary dengue infection), may develop a simple fever indistinguishable from other viral infections. Maculopapular rashes may accompany the fever or may appear during defervescence.

Upper respiratory and gastrointestinal symptoms are common

Dengue fever

After the incubation period, the illness begins abruptly and is followed by the three phases -- febrile, critical and recovery .

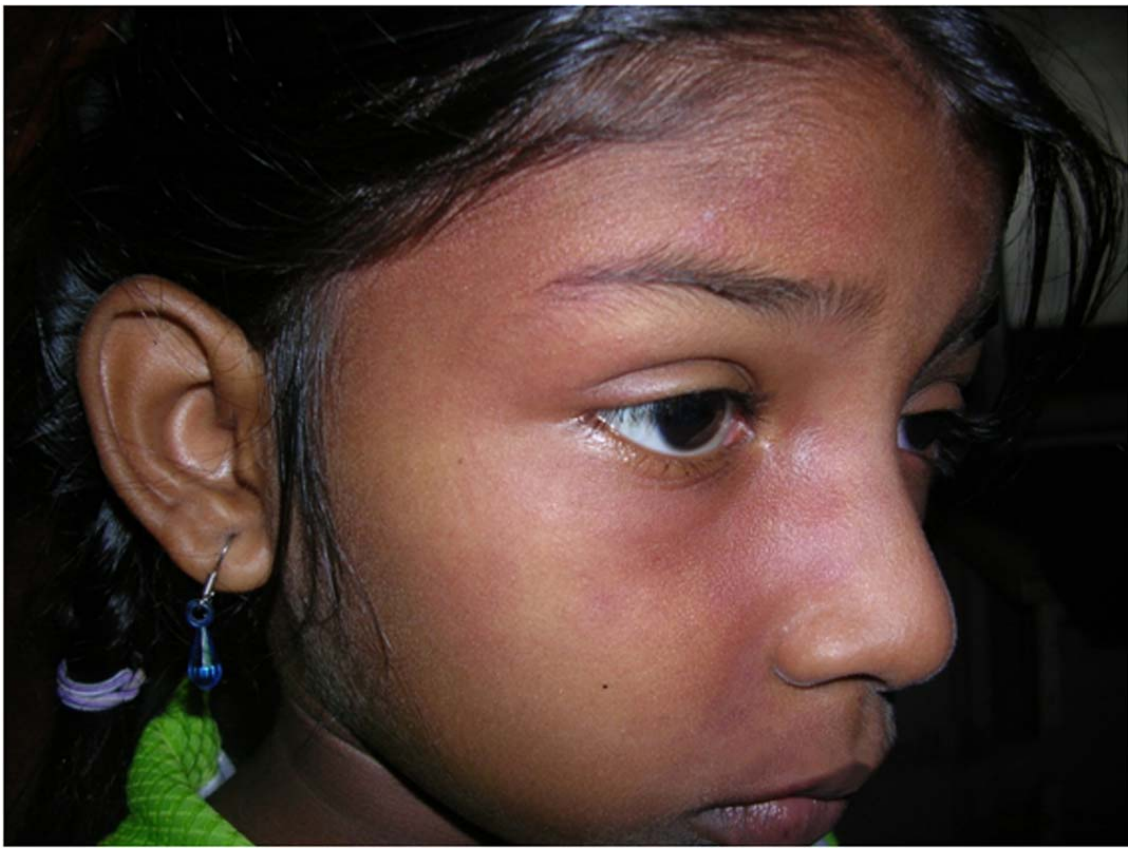
The course of dengue illness



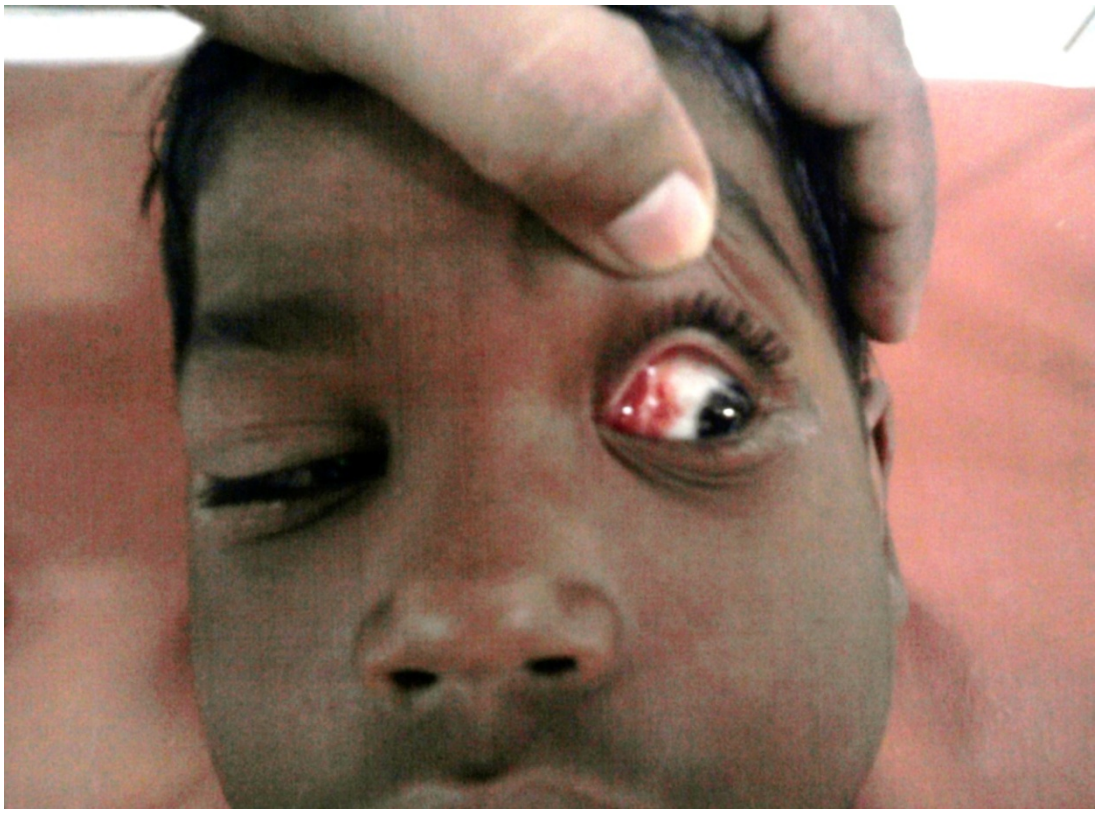
FEBRILE PHASE

Patients typically develop high-grade fever suddenly. This acute febrile phase usually lasts 2–7 days and is often accompanied by facial flushing, skin erythema, generalized body ache, myalgia, arthralgia and headache[13]. Some patients may have sore throat, injected pharynx and conjunctival injection. Anorexia, nausea and vomiting are common. It can be difficult to distinguish dengue clinically from non-dengue febrile diseases in the early febrile phase. A positive tourniquet test in this phase increases the probability of dengue [16]. In addition, these clinical features are indistinguishable between severe and non-severe dengue cases. Therefore monitoring for warning signs and other clinical

Facial flushing



Facial rash and Subconjuctival hemorrage



parameters is crucial.Mild haemorrhagic manifestations like petechiae and mucosal membrane bleeding(e.g. nose and gums) may be seen [17]. Massive vaginal bleeding (in women of childbearing age) and gastrointestinal bleeding may occur during this phase but is not common [18]. The liver is often enlarged and tender after a few days of fever[15]. The earliest abnormality in the full blood count is a progressive decrease in total white cell count, which should alert the physician to a high probability of dengue.

CRITICAL PHASE:

Around the time of defervescence, when the temperature drops to 37.5–38ºC or less and remains below this level, usually on days 3–7 of illness, an increase in capillary permeability in parallel with increasing haematocrit levels may occur[19] This marks the beginning of the critical phase. The period of clinically significant plasma leakage usually lasts 24–48 hours.

Progressive leukopenia [15] followed by a rapid decrease in platelet count usually precedes plasma leakage. At this point patients without an increase in capillary permeability will improve, while those with increased capillary permeability may become worse as a result of lost plasma volume. The degree of plasma leakage varies. Pleural effusion and ascites may be clinically detectable depending on the degree of plasma leakage and the volume of fluid therapy. Hence chest x-ray and abdominal ultrasound can be useful tools for

diagnosis. The degree of increase above the baseline haematocrit often reflects the severity of plasma leakage.

Shock occurs when a critical volume of plasma is lost through leakage. It is often preceded by warning signs. The body temperature may be subnormal when shock occurs. With prolonged shock, the consequent organ hypoperfusion results in progressive organ impairment, metabolic acidosis and disseminated intravascular coagulation. This in turn leads to severe haemorrhage causing the haematocrit to decrease in severe shock. Instead of the leukopenia usually seen during this phase of dengue, the total white cell count may increase in patients with severe bleeding. In addition, severe organ impairment such as severe hepatitis, encephalitis or myocarditis and/or severe bleedingmay also develop without obvious plasma leakage or shock [20].

Some patients progress to the critical phase of plasma leakage without defervescence and, in these patients, changes in the full blood count should be used to guide the onset of the critical phase and plasma leakage.

RECOVERY PHASE:

If the patient survives the 24–48 hour critical phase, a gradual reabsorption of extravascular compartment fluid takes place in the following 48–72 hours.

General well-being improves, appetite returns, gastrointestinal symptoms abate, Haemodynamic status stabilizes and diuresis ensues. Some patients may have a rash of “isles of white in the sea of red”[21]. Some may experience

generalized pruritus. Bradycardia and electrocardiographic changes are common during this stage.The haematocrit stabilizes or may be lower due to the dilutional effect of reabsorbed fluid. White blood cell count usually starts to rise soon after defervescence but the recovery of platelet count is typically later than that of white blood cell count.Respiratory distress from massive pleural effusion and ascites will occur at any time if excessive intravenous fluids have been administered. During the critical and/or recovery phases, excessive fluid therapy is associated with pulmonary oedema or congestive heart failure.

Febrile, critical and recovery phases in dengue

1	Febrile phase	Dehydration; high fever may cause neurological disturbances and febrile seizures in young children
2	Critical phase	Shock from plasma leakage; severe haemorrhage; organ impairment
3	Recovery phase	Hypervolaemia (only if intravenous fluid therapy has been excessive and/or has extended into this period)

Dengue hemorrhagic fever

DHF usually follows secondary dengue infections, but may sometimes follow pimary infections, especially in infants. In such infants, maternally acquired dengue antibodies are presumed to enhance primary infections [22]. Clinical deterioration usually occurs during defervescence (often between days 3 and 4). Tachycardia and hypotension characterize the onset of plasma leakage. When plasma leakage is severe patients may develop othersigns of circulatory disturbance such as prolonged capillary refill time, narrow pulse pressures, and shock. Inadequate treatment of such patients often leads to profound shock.In

DHF, bleeding may occur from any site and does not correlate with the platelet counts.

Haemorrhagic manifestations usually occur once the fever has settled.[23] Minor degrees of bleeding may manifest as gum bleeding and petechiae. The commonest site of haemorrhage is the gastrointestinal tract, which manifests as haematemesis or melaena, followed by epistaxis. Vaginal bleeding is commonly reported in females[21]. Convalescence in DHF is usually short and uneventful. The return of appetite is a good indicator of recovery.

Dengue shock syndrome

Dengue shock syndrome is associated with very high mortality (around 9.3%, increasing to 47% in instances of profound shock)[24]. Severe plasma leakage leading to dengue shock syndrome is associated with cold blotchy skin, circumoral cyanosis, and circulatory disturbances. Acute abdominal pain and persisting vomiting are early warning signs of impeding shock. Sudden hypotension may indicate the onset of profound shock .Prolonged shock is often accompanied by metabolic acidosis, which may precipitate disseminated intravascular coagulation or enhance ongoing disseminated intravascular coagulation, which in turn could lead to massive haemorrhage. Dengue shock syndrome may be accompanied by encephalopathy due to metabolic or electrolyte disturbances.

COMPLICATIONS:

DHF AND DSS have been associated with increasing frequency in recent times with the following complications[25]

System	Unusual or atypical manifestations
Neurological	Febrile seizures in young children. Encephalopathy. Encephalitis/aseptic meningitis. Intracranial haemorrhages/thrombosis. Subdural effusions. Mononeuropathies/polyneuropathies/Guillane-Barre Syndrome. Transverse myelitis.
Gastrointestinal/hepatic	Hepatitis/fulminant hepatic failure. Acalculous cholecystitis. Acute pancreatitis. Hyperplasia of Peyer's patches. Acute parotitis.
Renal	Acute renal failure. Hemolytic uremic syndrome.
Cardiac	Conduction abnormalities. Myocarditis. Pericarditis.
Respiratory	Acute respiratory distress syndrome. Pulmonary haemorrhage.
Musculoskeletal	Myositis with raised creatine phosphokinase (CPK). Rhabdomyolysis.
Lymphoreticular/bone marrow	Infection associated haemophagocytic syndrome. IAHS or Haemophagocytic lymphohistiocytosis (HLH), idiopathic thrombocytopenic purura (ITP). Spontaneous splenic rupture. Lymph node infarction.
Eye	Macular haemorrhage. Impaired visual acuity. Optic neuritis.
Others	Post-infectious fatigue syndrome, depression, hallucinations, psychosis, alopecia.

***Differential diagnoses of dengue*[26]**

- **Arboviruses:** Chikungunya virus (this has often been mistaken for dengue in South-East Asia).
- **Other viral diseases:** Measles; rubella and other viral exanthems; Epstein-Barr Virus (EBV); enteroviruses; influenza; hepatitis A; Hantavirus.
- **Bacterial diseases:** Meningococcaemia, leptospirosis, typhoid, melioidosis, rickettsial diseases, scarlet fever.
- **Parasitic diseases:** Malaria.

Pathogenesis of Dengue:

DHF occurs in a small proportion of dengue patients. Although DHF may occur in patients experiencing dengue virus infection for the first time, most DHF cases occur in patients with a secondary infection.[27] The association between occurrence of DHF/DSS and secondary dengue infections implicates the immune system in the pathogenesis of DHF. Both the innate immunity such as the complement system and NK cells as well as the adaptive immunity including humoral and cell mediated immunity are involved in this process[28]. Enhancement of immune activation, particularly during a secondary infection, leads to exaggerated cytokine response resulting in changes in vascular permeability. In addition, viral products such as NS1 may play a role in regulating complement activation and vascular permeability.[29]

The plasma leakage is unique in that there is selective leakage of plasma in the pleural and peritoneal cavities and the period of leakage is short (24–48 hours). Rapid recovery of shock without sequelae and the absence of inflammation in the pleura and peritoneum indicate functional changes in vascular integrity rather than structural damage of the endothelium as the underlying mechanism.Various cytokines with permeability enhancing effect have been implicated in the pathogenesis of DHF [30] .However, the relative importance of these cytokines in DHF is still unknown. Studies have shown that the pattern of cytokine response may be related to the pattern of cross-recognition of dengue-specific T-cells. Cross-reactive T-cells appear to be functionally deficit in their cytolytic activity but express enhanced cytokine production including TNF-a, IFN-g and chemokines[31].

Increase in vascular permeability can also be mediated by the activation of the complement system. Elevated levels of complement fragments have been documented in DHF.[32]Some complement fragments such as C3a and C5a are known to have permeability enhancing effects. In recent studies, the NS1 antigen of dengue virus has been shown to regulate complement activation and may play a role in the pathogenesis of DHF[27]

Higher levels of viral load in DHF patients in comparison with DF patients have been demonstrated in many studies[33]. The levels of viral protein, NS1, were also higher in DHF patients[34].The degrees of viral load correlate with measurements of disease severity.

High-risk patients

The following host factors contribute to more severe disease and its complications:

- infants and the elderly,
- obesity,
- pregnant women,
- peptic ulcer disease,
- women who have menstruation or abnormal vaginal bleeding,
- haemolytic diseases such as glucose-6-phosphatase dehydrogenase (G-6PD) deficiency,
- thalassemia and other haemoglobinopathies,
- congenital heart disease,
- chronic diseases such as diabetes mellitus, hypertension, asthma, ischaemic heart disease,
- chronic renal failure, liver cirrhosis,
- patients on steroid or NSAID treatment,

Laboratory Diagnosis

Rapid and accurate dengue diagnosis is of paramount importance for: (i) epidemiological surveillance;(ii) clinical management; (iii) research; and (iv) vaccine trials.Clinical management requires early diagnosis of cases, confirmation of clinical diagnosis and for differential diagnosis from other

flaviviruses/infection agents.The following laboratory tests are available to diagnose dengue fever and DHF:

- Virus isolation – serotypic/genotypic characterization
- Viral nucleic acid detection
- Viral antigen detection
- Immunological response based tests – IgM and IgG antibody assays
- Analysis for haematological parameters

Diagnostic tests and phases of disease

Dengue viraemia in a patient is short, typically occurs 2–3 days prior to the onset of fever and lasts for four to seven days of illness. During this period the dengue virus, its nucleic acid and circulating viral antigen can be detected Antibody response to infection comprises the appearance of different types of immunoglobulins and IgM and IgG immunoglobulin isotypes are of diagnostic value in dengue. IgM antibodies are detectable by days 3–5 after the onset of illness, rise quickly by about two weeks and decline to undetectable levels after 2–3 months. IgG antibodies are detectable at low level by the end of the first week, increase subsequently and remain for a longer period (for many years). Because of the late appearance of IgM antibody, i.e. after five days of onset of fever, serological tests based on this antibody done during the first five days of clinical illness are usually negative.

During the secondary dengue infection (when the host has previously been infected by dengue virus), antibody titres rise rapidly. IgG antibodies are

detectable at high levels, even in the initial phase, and persist from several months to a lifelong period. IgM antibody levels are significantly lower in secondary infection cases. Hence, a ratio of IgM/IgG is commonly used to differentiate between primary and secondary dengue infections. Thrombocytopenia is usually observed between the third and eighth day of illness followed by other haematocrit changes.

Isolation of virus

Isolation of dengue virus from clinical specimens is possible provided the sample is taken during the first six days of illness and processed without delay. Specimens that are suitable for virus isolation include: acute phase serum, plasma or washed buffy coat from the patient, autopsy tissues from fatal cases (especially liver, spleen, lymph nodes and thymus), and mosquitoes collected from the affected areas Currently, cell culture is the most widely used method for dengue virus isolation. The mosquito cell line C6/36 or AP61 are the host cells of choice for isolation of dengue viruses.

Viral nucleic acid detection

Dengue viral genome, which consists of ribonucleic acid (RNA), can be detected by reverse transcripatse polymerase chain reaction (RT-PCR) assay.

Nested RT-PCR

Nested RT-PCR assay involves using universal dengue primers targeting the C/prM region of the viral genome for an initial reverse transcription and

amplification step, followed by a nested PCR amplification that is serotype-specific.

One-step multiplex RT-PCR

This test is an alternative to nested RT-PCR. A combination of the four serotype - specific reactions are separated by electrophoresis on an agarose gel, and the amplification products are visualized as bands of different molecular weights after staining the gel using ethidium bromide dye, and compared with standard molecular weight markers. In this assay, dengue serotypes are identified by the size of their bands.

Real-time RT-PCR

The real-time RT-PCR assay is also a one-step assay system using primer pairs and probes that are specific to each dengue serotype. The use of a fluorescent probe enables the detection of the reaction products in real time.The test is very useful for large-scale surveillance.

Isothermal amplification method

The NASBA (nucleic acid sequence-based amplification) assay is an isothermal RNA-specific amplification assay that does not require thermal cycling instrumentation.

Compared with virus isolation, the sensitivity of the RT-PCR methods varies from 80% to 100% and depends upon the region of the genome targeted by the primers, the approach used to amplify or detect PCR products and the methods employed for subtyping. The advantages of this technology include

high sensitivity and specificity, ease of identifying serotypes and early detection of the infection. It is, however, an expensive technology.

Recently, Loop Mediated Amplification (LAMP) PCR method has been developed, which promises an easy-to-do and less expensive instrumentation alternative for RT-PCR and real-time PCR assays.

Viral antigen detection

The NS1 gene product is a glycoprotein produced by all flaviviruses and is essential for replication and viability of the virus. The protein is secreted by mammalian cells but not by insect cells. NS1 antigen appears as early as Day 1 after the onset of the fever and declines to undetectable levels by 5–6 days. Hence, tests based on this antigen can be used for early diagnosis.ELISA and dot blot assays directed against the envelop/membrane (EM) antigens and non-structural protein 1 (NS1) demonstrated that this antigen is present in high concentrations in the sera of the dengue virus-infected patients during the early clinical phase of the disease and can be detected in both patients with primary and secondary dengue infections for up to six days after the onset ofthe illness. Commercial kits for the detection of NS1 antigens are now available; however, these kits do not differentiate between the serotypes

Immunological response and serological tests

Five basic serological tests are used for the diagnosis of dengue infection.

IgM-capture enzyme-linked immunosorbent assay (MAC-ELISA)

MAC-ELISA has become widely used in the past few years. It is a simple and rapid test that requires very little sophisticated equipment. MAC-ELISA is based on detecting the dengue-specific IgM antibodies in the test serum by capturing them out of solution using anti-human IgM that was previously bound to the solid phase[35]. If the patient's serum has antidengue IgM antibody, it will bind the dengue antigen that is added in the next step and can be detected by subsequent addition of an enzyme-labelled anti-dengue antibody, which may be human or monoclonal antibody. An enzyme-substrate is added to produce a colour reaction.

The anti-dengue IgM antibody develops a little earlier than IgG, and is usually detectable by Day5 of the illness, i.e. the antibody is not usually detectable during the first five days of illness. However,the time of appearance of IgM antibody varies considerably among patients. IgM antibody titers in primary infections are significantly higher than in secondary infections, although it is not uncommon to obtain IgM titers of 320 in the latter cases. In some primary infections, detectable IgM may persist for more than 90 days, but in most patients it wanes to an undetectable level by 60 days MAC-ELISA is slightly less sensitive than the HI test for diagnosing dengue infection. MAC-ELISA has become an invaluable tool for surveillance of DF, DHF and DSS.It is especially useful for hospitalized patients who are generally admitted at a late stage of illness after detectable IgM is already present in the blood.

IgG-ELISA

An indirect IgG-ELISA has been developed and compares well with the HI test.This test can also be used to differentiate primary and secondary dengue infection

Interpretation of dengue diagnostic tests (adapted from Dengue and Control (DENCO) study

Highly suggestive	Confirmed
One of the following: 1. IgM + in a single serum sample 2. IgG + in a single serum sample with a HI titre of 1280 or greater	One of the following: 1. PCR + 2. Virus culture + 3. IgM seroconversion in paired sera 4. IgG seroconversion in paired sera or fourfold IgG titer increase in paired sera

IgM/IgG ratio

The IgM/IgG ratio is used to distinguish primary infection from secondary dengue infection . A dengue virus infection is defined as primary if the capture IgM/IgG ratio is greater than 1.2, or as secondary if the ratio is less than 1.2

Haemagglutination inhibition test

Of the above tests, haemagglutination inhibition or HI test has been most frequently used in the past for routine serological diagnosis of dengue infections. It is sensitive and easy to perform, requires only minimal equipment HI antibodies persist for longperiods (up to 50 years or longer), the test is ideal for sero-epidemiologic studies

Complement fixation test

The *complement fixation or* CF test is not widely used for routine dengue diagnostic serology. It is more difficult to perform and requires highly trained personnel.

Neutralization test

The *neutralization test or* NT is the most specific and sensitive serological test for dengue viruses used for determining the immune protection. The common protocol used in most dengue laboratories is the serum dilution plaque reduction neutralization test (PRNT)

Rapid diagnostic test (RDT)

A number of commercial rapid format serological test-kits for anti-dengue IgM and IgG antibodies have become available in the past few years, some of these producing results within 15 minutes[36].Unfortunately, the accuracy of most of these tests is uncertain since they have not yet been properly validated. Rapid tests can yield false positive results due to cross-reaction with other flaviviruses, malaria parasite, leptospires and immune disorders such as rheumatoid and lupus.

Haematological tests

Standard haematological parameters such as platelet count and haematocrit are important and are part of the biological diagnosis of dengue infection. Therefore, they should be closely monitored.

Thrombocytopenia, a drop in platelet count below 100 000 per µl, may be occasionally observed in dengue fever but is a constant feature in DHF. Thrombocytopenia is usually found between the third and eighth day of illness often before or simultaneously with changes in haematocrit.

Haemoconcentration with an increase in the haematocrit of 20% or more (for the same patient or for a patient of the same age and sex) is considered to be a definitive evidence of increased vascular permeability and plasma leakage.

Basic metabolic panel findings include the following:

Hyponatremia is the most common electrolyte abnormality observed in patients with DHF or DSS.

Metabolic acidosis is observed in those with shock, and it must be corrected rapidly.

Elevated BUN is observed in those with shock.

Liver function test findings include the following:

Mild elevations in transaminase levels may be seen.

Low albumin is a sign of hemoconcentration

Diagnostic methods	Diagnosis of acute infection	Time to results	Specimen	Time of collection after onset of symptoms	Facilities
Viral isolation and serotype identification	Confirmed	1–2 weeks	Whole blood, serum, tissues	1–5 days	Mosquito or cell culture facilities, BSL-2/BSL-3[a] laboratory, fluorescence microscope or molecular biology equipment
Nucleic acid detection	Confirmed	1 or 2 days	Tissues, whole blood, serum, plasma	1–5 days	BSL-2 laboratory, equipment for molecular biology
Antigen detection	Not yet determined Confirmed	1 day >1 day	Serum Tissue for immuno-chemistry	1–6 days NA	ELISA facilities Facilities for histology
IgM ELISA	Probable	1–2 days	Serum, plasma, whole blood	After 5 days	ELISA facilities
IgM rapid test		30 minutes			No additional supplies
IgG (paired sera) by ELISA, HI or neutralization test	Confirmed	7 days or more	Serum, plasma, whole blood	Acute sera, 1–5 days; convalescent after 15 days	ELISA facilities BSL-2 laboratory for neutralization assay

CASE DEFINITION[2]

DENGUE FEVER:is defined by

Acute febrile illness with two or more of the following[l]:

- headache,
- retro-orbital pain,
- myalgia,
- arthralgia/bone pain,
- rash,
- haemorrhagic manifestations,
- leucopenia (wbc ≤5000 cells/mm³),
- thrombocytopenia (platelet count <150 000 cells/mm³),
- rising haematocrit (5 – 10%);

and at least one of following:

- supportive serology on single serum sample: titre ≥1280 with haemagglutination inhibition test, comparable IgG titre with enzyme-linked immunosorbent assay, or tasting positive in IgM antibody test, and
- occurrence at the same location and time as confirmed cases of dengue fever.

Confirmed diagnosis:

Probable case with at least one of the following:

- isolation of dengue virus from serum, CSF or autopsy samples.
- fourfold or greater increase in serum IgG (by haemagglutination inhibition test) or increase in IgM antibody specific to dengue virus.
- detection of dengue virus or antigen in tissue, serum or cerebrospinal fluid by immunohistochemistry, immunofluorescence or enzyme-linked immunosorbent assay.
- detection of dengue virus genomic sequences by reverse transcription-polymerase chain reaction.

DENGUE HEMORRHAGIC FEVER: is defined by

All of following[m]:

- acute onset of fever of two to seven days duration.
- haemorrhagic manifestations, shown by any of the following: positive tourniquet test, petechiae, ecchymoses or purpura, or bleeding from mucosa, gastrointestinal tract, injection sites, or other locations.
- platelet count ≤100 000 cells/mm³
- objective evidence of plasma leakage[n] due to increased vascular permeability shown by any of the following:
  - Rising haematocrit/haemoconcentration ≥20% from baseline or decrease in convalescence, or evidence of plasma leakage such as pleural effusion, ascites or hypoproteinaemia/albuminaemia.[39]

DENGUE SHOCK SYNDROME:is defined by

Criteria for dengue haemorrhagic fever as above with signs of shock including:

- tachycardia, cool extremities, delayed capillary refill, weak pulse, lethargy or restlessness, which may be a sign of reduced brain perfusion.
- pulse pressure ≤20 mmHg with increased diastolic pressure, e.g. 100/80 mmHg.
- hypotension by age, defined as systolic pressure <80 mmHg for those aged <5 years or 80 to 90 mmHg for older children and adults.

SEVERITY GRADING OF DENGUE:

WHO classification of dengue infections and grading of severity of DHF

DF/ DHF	Grade	Signs and Symptoms	Laboratory
DF		Fever with two of the following: • Headache. • Retro-orbital pain. • Myalgia. • Arthtralgia/bone pain. • Rash. • Haemorrhagic manifestations. • **No evidence of plasma leakage.**	• Leucopenia (wbc ≤5000 cells/mm³). • Thrombocytopenia (Platelet count <150 000 cells/mm³). • Rising haematocrit (5% – 10%). • No evidence of plasma loss.
DHF	I	Fever and haemorrhagic manifestation (positive tourniquet test) and **evidence of plasma leakage**	Thrombocytopenia <100 000 cells/ mm³; HCT rise ≥20%
DHF	II	As in Grade **I plus** spontaneous bleeding.	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%.
DHF#	III	As in Grade **I or II plus** circulatory failure (weak pulse, narrow pulse pressure (≤20 mmHg), hypotension, restlessness).	Thrombocytopenia <100 000 cells/mm³; HCT rise ≥20%.
DHF#	IV	As in Grade **III** plus profound shock with undetectable BP and pulse	Thrombocytopenia < 100 000 cells/mm³; HCT rise ≥20%.

MANAGEMENT

Disease notification

In dengue-endemic countries, cases of suspected, probable and confirmed dengue should be notified as soon as possible so that appropriate public health measures can be initiated . Laboratory confirmation is not necessary before notification, but should be obtained. In non-endemic countries, usually only confirmed cases will be notified. Suggested criteria for early notification of suspected cases are that the patient lives in or has travelled to a dengue-endemic area, has fever for three days or more, has low or decreasing white cell counts, and/or has thrombocytopenia ± positive tourniquet test. In dengue-endemic countries, the later the notification, the more difficult it is to prevent dengue transmission.

Treatment of Dengue & DHF[2]:

Febrile Phase:

In the initial phase the treatment of DF & DHF is the same and is as that of any other viral fever, i.e. symptomatic and supportive.

- Rest.
- **Paracetamo**l (not > than 4 times in 24 hrs) according to age and weight for fever above 39°C.
- **Do not** give Aspirin or Brufen. Aspirin can cause gastritis and/or bleeding. In children, Reye's syndrome (Encephalopathy) may be a serious complication.

 Do not give antibiotics as these do not help.

 Oral Rehydration Therapy is recommended as there may be mild to moderate Dehydration due to vomiting & high temperature.

 Food can be given as per appetite.

Dengue Hemorrhagic Fever

Patients with known or suspected DF should have their platelet count and Hematocrit measured daily from the third day of illness until 1-2 days after defervescence. Those patients with a rising hematocrit or falling platelet count should have intravascular volume deficits replaced. Those patients who improve can continue to be monitored in an outpatient setting. Those patients who do not improve should be admitted to the hospital for continued hydration.

Other **indications of Hospitalization** include:

 Patients who develop signs of Tachycardia

 ↑ CRT (> 2 sec)

 Cool and clammy extremities

 Diminished peripheral pulses

 Changes in Mental status

 Oliguria

 Sudden rise in hematocrit

 Narrowing of pulse pressure (< 20 mm Hg)

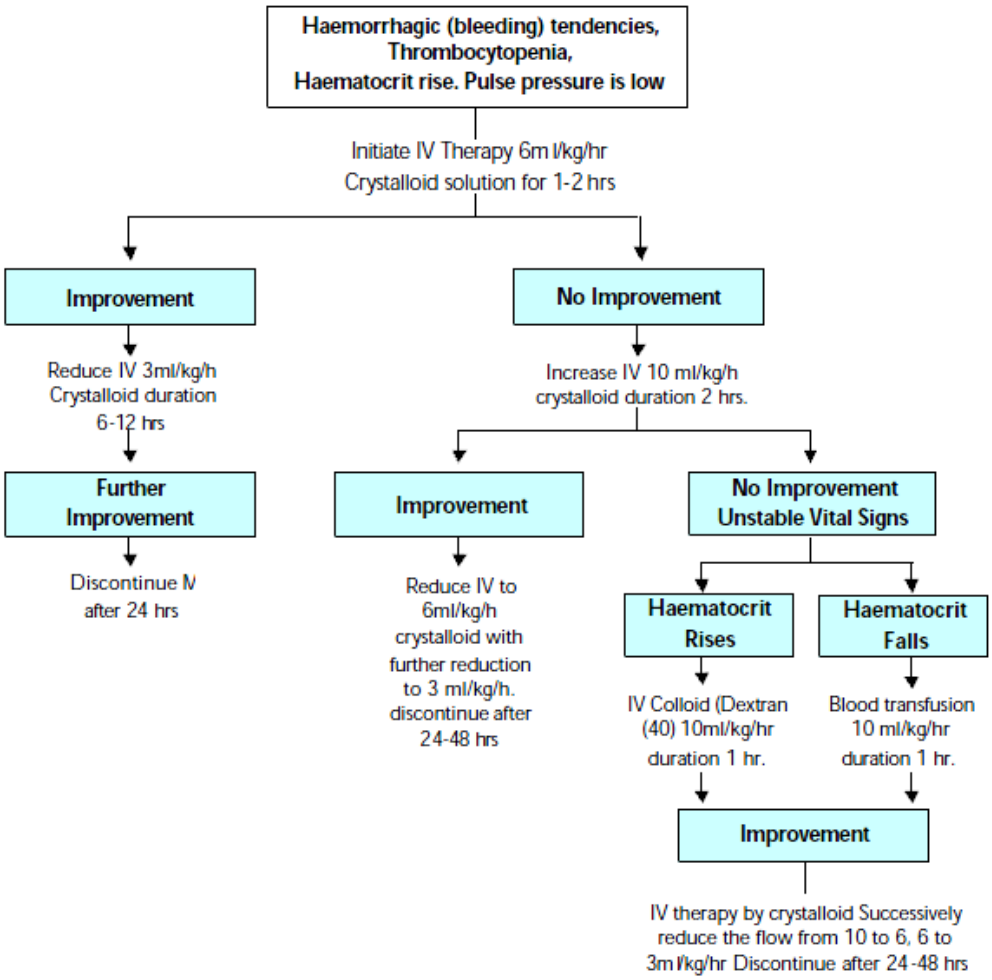
 Hypotension (Late finding-Uncorrected shock)

Intravascular volume deficits should be corrected with isotonic fluids such as Ringer lactate solution. Boluses of 10-20 ml/kg should be given over 20 minutes and may be repeated. If this fails to correct the deficit, the hematocrit value should be determined, and, if it is rising, limited clinical information suggests that a plasma expander may be administered. Starch, dextran 40, or albumin 5% at a dose of 10-20 ml/kg may be used. If the patient does not improve after this, blood loss should be considered. Patients with internal or gastrointestinal bleeding may require transfusion. Patients with coagulopathy may require fresh frozen plasma.

After patients with dehydration are stabilized, they usually require intravenous fluids for no more than 24-48 hours. Intravenous fluids should be stopped when the hematocrit level falls below 40% and adequate intravascular volume is present. At this time, patients reabsorb extravasated fluid and are at risk for volume overload if intravenous fluids are continued. Do not interpret a falling hematocrit value in a clinically improving patient as a sign of internal bleeding.

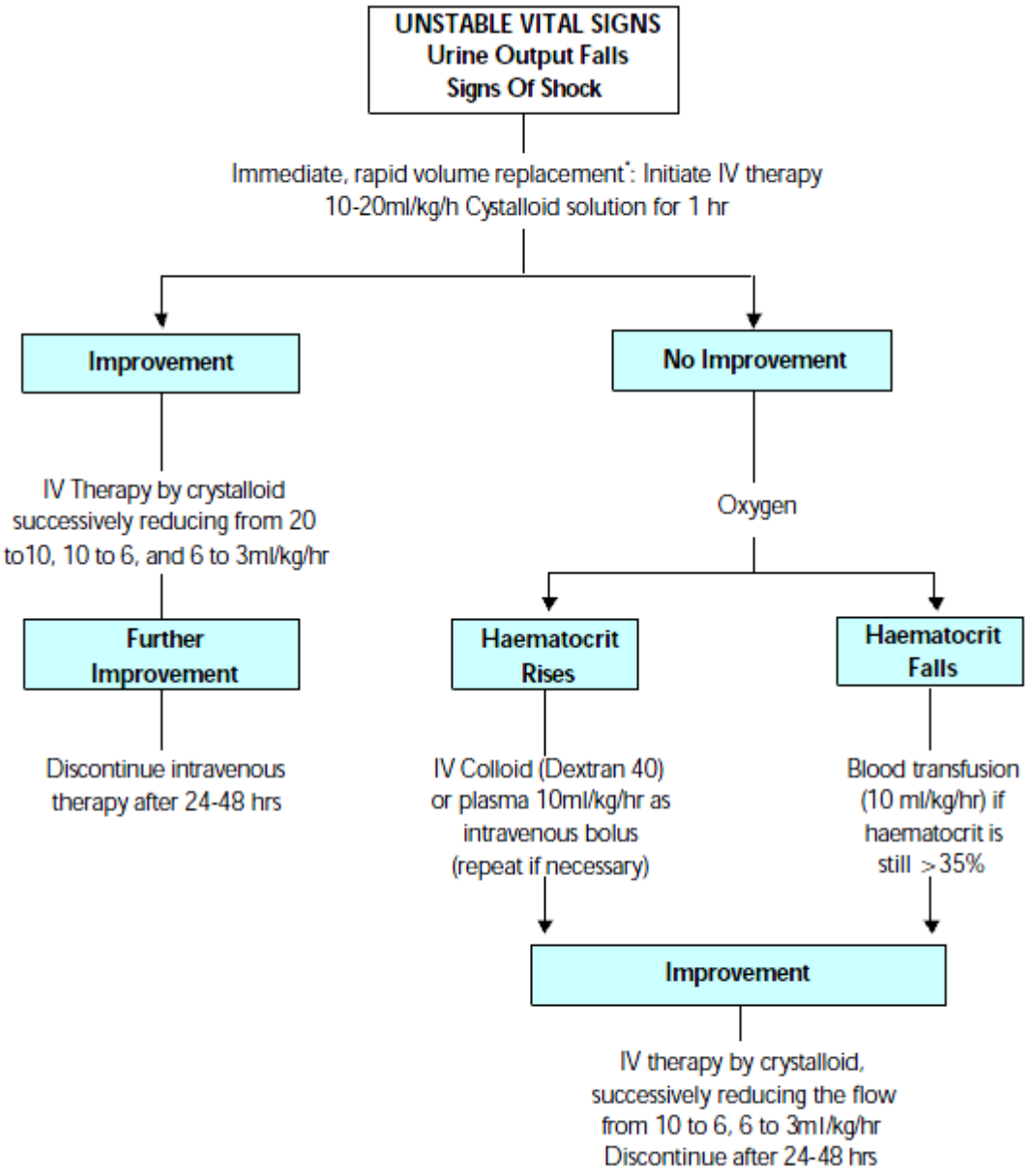
Fluid therapy

DENGUE GRADE 1,II



DENGUE GRADE III,IV

UNSTABLE VITALS



Fluids Recommended:

Crystalloids :

- ☐ 5% Dextrose in Isotonic NS
- ☐ 5% Dextrose in 1/2 NS
- ☐ 5% Dextrose in RL
- ☐ Shock Correction NS or RL

Colloids :

- ☐ Dextran 40
- ☐ Hemaccel
- ☐ Plasma

Fluid Replacement

- ☐ Volume of fluid to be just sufficient to maintain effective circulation during plasma leakage.
- ☐ Fluid charts to be made every 1 to 3 hrs and even more frequently in shock.
- ☐ Change should not be drastic. e.g. don't jump from 20 ml to 6ml or vice versa. Go in a step wise manner.

Indications of Platelet / Whole blood transfusion[2]

Platelets

- ☐ Platelet count < 20,000/ cu.mm
- ☐ Platelet count >20,000 <40,000 with hemorrhagic manifestations.
- ☐ DIC

Whole Blood

- ☐ Prolonged refractory shock with ↓↓HCT even with adequate fluid replacement
- ☐ Severe massive bleeding (> 10 % of total blood volume).

Indications of FFP

(Fresh frozen Plasma)

- ☐ Plasma is used when HCT is rising despite fluid replacement
- ☐ But plasma substitutes are equally good (Dextran 40) & effective
- ☐ Essential only in cases of massive bleeding with DIC.

Monitoring of patients in DSS

- ☐ Check vitals every 15-30 minutes until shock is overcome.
- ☐ Check HCT / Platelets for every 2 hours for the first 6 hours and every 4 hours until stable.
- ☐ Fluid balance sheet to be maintained. Frequency & volume of urine output to be recorded. In refractory shock catheter may be needed.

Criteria for Discharge[2]

Patients who are resuscitated from shock recover rapidly. Patients with DHF or dengue shock syndrome (DSS) may be discharged from the hospital when they meet the following criteria:

- ☐ Afebrile for 24 hours without antipyretics
- ☐ Good appetite, clinically improved condition
- ☐ Adequate urine output

- ☐ Stable hematocrit
- ☐ At least 48 hours have passed since recovery from shock
- ☐ Absence of respiratory distress
- ☐ Platelet count greater than 50,000.

Management of high-risk patients

- ☐ Obese patients have less respiratory reserves and care should be taken to avoid excessive intravenous fluid infusions. The ideal body weight should be used to calculate fluid resuscitation and replacement and colloids should be considered in the early stages of fluid therapy. Once stabilized, furosemide may be given to induce diuresis.
- ☐ Infants also have less respiratory reserves and are more susceptible to liver impairment and electrolyte imbalance. They may have a shorter duration of plasma leakage and usually respond quickly to fluid resuscitation. Infants should, therefore, be evaluated more frequently for oral fluid intake and urine output.
- ☐ Intravenous insulin is usually required to control the blood sugar levels in dengue patients with diabetes mellitus. Non-glucose containing crystalloids should be used.
- ☐ Patients with hypertension may be on anti-hypertensive therapy that masks the cardiovascular response in shock. The patient's own baseline blood pressure should be considered. A blood pressure that is perceived to be normal may in fact be low for these patients.

- ☐ Anti-coagulant therapy may have to be stopped temporarily during the critical period.
- ☐ Haemolytic diseases and haemoglobiopathies : These patients are at risk of haemolysis and will require blood transfusion. Caution should accompany hyper hydration and alkalinisation therapy, which can cause fluid overload and hypo calcemia.
- Congenital and ischemic heart diseases: Fluid therapy should be more cautious as they may have less cardiac reserves.
- ☐ For patients on steroid therapy, continued steroid treatment is recommended but the route may be changed.

Management of complications

The most common complication is fluid overload

Detection of fluid overload in patients

- ☐ Early signs and symptoms include puffy eyelids, distended abdomen (ascites), tachypnoea, mild dyspnoea.
- ☐ Late signs and symptoms include all of the above, along with moderate to severe respiratory distress, shortness of breath and wheezing (not due to asthma) which are also an early sign of interstitial pulmonary oedema and crepitations. Restlessness/agitation and confusion are signs of hypoxia and impending respiratory failure.

Management of fluid overload

All hypotonic solutions should be stopped. In the early stage of fluid overload, switch from crystalloid to colloid solutions as bolus fluids. Dextran 40 is effective as 10 ml/kg bolus infusions, but the dose is restricted to 30 ml/kg/day because of its renal effects. Dextran 40 is excreted in the urine and will affect urine osmolarity. Patients may experience “sticky” urine because of the hyperoncotic nature of Dextran 40 molecules (osmolarity about twice that of plasma). Voluven may be effective (osmolarity = 308 mosmole) and the upper limit is 50ml/kg/day. However, no studies have been done to prove its effectiveness in cases of DHF/DSS. In the late stage of fluid overload or those with frank pulmonary oedema, furosemide may be administered if the patient has stable vital signs. If they are in shock, together with fluid overload 10 ml/kg/h of colloid (dextran) should be given. When the blood pressure is stable, usually within 10 to 30 minutes of infusion, administer IV 1 mg/kg/dose of furosemide and continue with dextran infusion until completion. Intravenous fluid should be reduced to as low as 1 ml/kg/h until discontinuation when haematocrit decreases to baseline or below (with clinical improvement). The following pointsshould be noted:

- ☐ These patients should have a urinary bladder catheter to monitor hourly urine output.

- ☐ Furosemide should be administered during dextran infusion because the hyperoncotic nature of dextran will maintain the intravascular volume while furosemide depletes in the intravascular compartment.
- ☐ **After administration of furosemide, the vital signs should be monitored every 15 minutes for one hour to note its effects.**
- ☐ If there is no urine output in response to furosemide, check the intravascular volume status (CVP or lactate). If this is adequate, pre-renal failure is excluded, implying that the patient is in an acute renal failure state. These patients may require ventilatory support soon..
- ☐ In cases with no response to furosemide (no urine obtained), repeated doses of furosemide and doubling of the dose are recommended. If oliguric renal failure is established, renal replacement therapy is to be done as soon as possible. These cases have poor prognosis.
- ☐ Pleural and/or abdominal tapping may be indicated and can be life-saving in cases with severe respiratory distress and failure of the above management. This has to be done with extreme caution because traumatic bleeding is the most serious complication and leads to death.

Management of encephalopathy

Some DF/DHF patients present unusual manifestations with signs and symptoms of central nervous system (CNS) involvement, such as convulsion and/or coma. This has generally been shown to be encephalopathy, not encephalitis, which may be a result of intracranial haemorrhage or occlusion

associated with DIC or hyponatremia. CNS infections documented by virus isolations from the cerebrospinal fluid (CSF) or brain.

Most of the patients with encephalopathy report hepatic encephalopathy. The principal treatment of hepatic encephalopathy is to prevent the increase of intracranial pressure (ICP).Radiological imaging of the brain (CT scan or MRI) is recommended if available to rule out intracranial haemorrhage. The following are recommendations for supportive therapy for this condition:

- Maintain adequate oxygenation with oxygen therapy. Prevent/reduce ICP by the following measures:
    - give minimal IV fluid to maintain adequate intravascular volume; ideally the total IV fluid should not be >80% fluid maintenance.
    - switch to colloidal solution earlier if haematocrit continues to rise and a large volume of IV is needed in cases with severe plasma leakage.
    - administer a diuretic if indicated in cases with signs and symptoms of fluid overload.
    - positioning of the patient must be with the head up by 30 degrees.
    - early intubation to avoid hypercarbia and to protect the airway.
    - may consider steroid to reduce ICP. Dexamethazone 0.15 mg/kg/dose IV to be administered every 6–8 hours.
- Decrease ammonia production by the following measures:

- give lactulose 5–10 ml every six hours for induction of osmotic diarrhoea.
- local antibiotic gets rid of bowel flora; it is not necessary if systemic antibiotics are given.

☐ Maintain blood sugar level at 80–100 mg/dl per cent. Recommend glucose infusion rate is anywhere between 4–6 mg/kg/hour.

☐ Correct acid-base and electrolyte imbalance, e.g. correct hypo/hypernatremia, hypo/hyperkalemia, hypocalcemia and acidosis.

☐ Vitamin K1 IV administration; 3 mg for <1-year-old, 5 mg for <5-year-old and 10 mg for>5-year-old and adult patients.

☐ Anticonvulsants should be given for control of seizures: phenobarbital, dilantin and diazepam IV as indicated.

☐ Transfuse blood, preferably freshly packed red cells, as indicated. Other blood components such as as platelets and fresh frozen plasma may not be given because the fluid overload may cause increased ICP.

☐ Empiric antibiotic therapy may be indicated if there are suspected superimposed bacterial infections.

☐ H2-blockers or proton pump inhibitor may be given to alleviate gastrointestinal bleeding.

☐ Avoid unnecessary drugs because most drugs have to be metabolized by the liver.

- ☐ Consider plasmapheresis or haemodialysis or renal replacement therapy in cases with clinical deterioration.

VECTOR CONTROL

Environmental management methods[37]

- ☐ Environmental modification: This includes any long-lasting physical transformation of land, water and vegetation aimed at reducing vector habitats without causing unduly adverse effects on the quality of the human environment.
- ☐ Environmental manipulation: This incorporates planned recurrent activities aimed at producing temporary changes in vector habitats that involve the management of "essential" and "non-essential" containers, and the management or removal of "natural" breeding sites.such as

1. improved water supply
2. covering of overhead tanks
3. land filling, levelling

- ☐ Changes to human habitation or behaviour: These feature the efforts made to reduce man-vector-virus contact.

Biological control

Biological control is based on the introduction of organisms that prey upon, reduce populations of the target species. The application of biological control agents, which are directed against the larval stages of dengue vectors, While biological control avoids chemical contamination of the environment,

Larvivorus fish (*Gambusia affinis* and *Poecilia reticulata*) have been extensively used for the control of *An. stephensi* and/or *Ae. aegypti* in large water bodies or large water containers in many countries. Two species of endotoxin-producing bacteria, *Bacillus thuringiensis* serotype H-14 and *Bacillus sphaericus* are effective mosquito control agents. Copepods have a role in dengue vector control,

Chemical control

Chemicals have been used to control *Ae. aegypti* since the beginning of the 20th century. *Aedes* larval habitats were treated with oil and homes were fumigated with pyrethrins DDT emerged in the early 1960s, organophosphate insecticides, including fenthion, malathion and fenitrothion, were used for *Ae. aegypti* adult control and temephos as a larvicide. Current methods are larvicide application and space spraying. Larviciding or "focal" control of *Ae. aegypti* is usually limited to domestic-use containers that cannot be destroyed, eliminated or otherwise managed. It is difficult and expensive to apply chemical larvicides on a long-term basis. Therefore, chemical larvicides are best used in situations where the disease and vector surveillance indicate the existence of certain periods of high risk and in localities where outbreaks might occur

Personal protection

Protective clothing

Clothing reduces the risk of mosquito bite if the cloth material is sufficiently thick or loosely fitting. Long sleeves and trousers with stockings may protect the arms and legs, which are the preferred sites for mosquito bites. Schoolchildren should adhere to these practices whenever possible Household insecticidal products, namely mosquito coils and aerosols, are used extensively for personal protection against mosquitoes. Repellents are common means of personal protection against mosquitoes and other biting insects .Insecticide-treated mosquito nets (ITNs) have limited utility in dengue control programmes since the vector species bites during the day.

METHODOLOGY

Type of Study: Cross Sectional Study.

Study Period: The study was conducted from Dec 2009 to Dec 2010.

Settings: Children less than 12 years of age with clinical features of Dengue (any acute febrile illness with two of the following: myalgia, head ache, retro-orbital pain, bleeding, altered sensorium, shock or low platelet count) admitted at Children Medical Ward of Tirunelveli Medical College Hospital during the study period were registered in the study. Informed consent was obtained and detailed history was taken. For all cases, the rapid Ig M ELISA test was done at our hospital. Children positive for Ig M were followed up for clinical profile.

Sample Size: From Dec 2009 to Dec 2010, there were totally 53 cases according to the inclusion and exclusion criteria.

Inclusion Criteria:

- Children less than 12 years of age with clinical features of dengue (any acute febrile illness) with two of the following :
    - Rash
    - Headache
    - Myalgia/ Arthralgia
    - Bleeding manifestation
    - Altered sensorium
    - Retro orbital pain
    - Shock or low platelet count

Exclusion Criteria:

- Clinical Features suggestive of Dengue with other serology positive cases.

Tools used:

Using Proforma the basic socio demographic details, Clinical features were collected. Laboratory investigations carried out in these patients include Haemoglobin, Complete blood count, Dengue IgM serology, Liver function test, serum amylase. Chest X ray was taken to demonstrate pleural effusion. Ultrasound abdomen was done to identify ascites, polyserositis and gall bladder wall thickening. CSF analysis was done in patients with convulsions, meningeal signs and altered sensorium.

Outcome Measures: Children positive for IgM were followed for the clinical profile and outcome.

The number of children included based on the above criteria was 53. Children who were seropositive were classified on the basis of WHO criteria as follows:

1. Dengue fever (DF): dengue seropositive without bleed.
2. Dengue fever with unusual bleed (DFB): dengue seropositive with bleeding tendencies, not satisfying WHO criteria for DHF
3. Dengue haemorrhagic fever (DHF): Dengue seropositive with bleeds with evidence of plasma leakage.

4. Dengue Shock Syndrome (DSS): DHF with evidence of peripheral circulatory failure.

Data Analysis:

Data collected were entered in Excel Spreadsheet and analysed using SPSS Version 16. Simple calculations like Percentages, Proportions and Mean values were derived. Appropriate statistical tests like Chi – Square test, T test were used.

OBSERVATION &RESULTS

53 sero positive dengue cases were reported in our hospital during study period.

Dengue fever:11(20.8%)

Dengue hemorrhagic fever:29 (54.7%)

Dengue shock syndrome:13(24.5%)

TABLE 1

CLINICAL FEATURES:

NO	FEATURES	TOTAL (n=53)	DF(n=11)	DHF(n=29)	DSS(n=13)	P value
1	Mean Age(yr)(±SD)	6.6(±3.8)	6.05(±4.2)	7.0(±3.4)	6.4(±4.5)	0.35
2	Age yrs <1 year	9(17%)	2(18.2%)	3(10.3%)	4(30.8%)	
3	Age 1-5 years	11(20.8%)	4(36.4%)	6(20.7%)	1(7.7%)	
4	Age 6-12 years	33(62.3%)	5(45.4%)	20(69%)	8(61.5%)	
5	Mean duration of fever (±SD)	6.02(±2.7)	6.18(±3.7)	6.21(±2.3)	5.46(±3.01)	
6	Female sex no.,%	27(50.9%)	6(54.5%)	15(51.7%)	6(46.2%)	

The age group of the affected children were between 6 months to 12 years.(Mean 6.6 yrs ,standard deviation 3.8). Infants comprised 17% of total

study group. 20.8% were children between 1 and 5 years of age. 62.3% were children between 6 and 12 years.DHF and DSS was found to be more common in 6-12 years age group. But this fact is not statistically significant. Mean duration of fever was 6.02 days. It was 6.18,6.21,5.46 days in DF, , DHF, DSS respectively. Males(49.1%) and females(50.9%) were comparatively equally affected.

TABLE 2

CLINICAL FEATURES

No	Features	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P VALUE
1	ABDOMINAL PAIN	22(41.5%)	2(18.2%)	18(62.1%)	2(15.4%)	0.004
2	VOMITING	36(67.9%)	8(72.7%)	20(69%)	8(61.5%)	0.82
3	DIARRHOEA	10(18.9%)	2(18.2%)	1(3.4%)	7(53.8%)	0.001
4	SEIZURE	6(11.3%)	1(9.1%)	0	5(38.5%)	0.001
5	COUGH	14(26.4%)	1(9.1%)	9(31%)	4(30.8%)	0.342

Most common symptoms were fever 100%, vomiting 67.9% and Abdominal pain 41.5%. Fever was present in all children. Abdominal pain was common in DHF (62.1%) when compared to DF (18.2%) and DSS (15.4).It is statistically significant P=0.004.Diarrhoea was more common in DSS (53.8%) compared to DF and DHF. It is statistically significant. SEIZURE was common

in DSS(38.5%) while none of the DHF cases had seizure. Both are statistically significant.

TABLE 3

CLINICAL FEATURES

No	Features	TOTAL(n=53)	DF(n=11)	DHF(n=29)	DSS(n=13)	P VALUE
1	Rash	20(37.7%)	4(36.4%)	11(37.9%)	5(38.5%)	0.9
2	GI BLEED	18(34%)	0	11(37.9%)	7(53.8%)	0.017
3	POSITIVE HESSTEST	10(18.9%)	0	6(20.7%)	4(30.8%)	0.148

GI bleed was present in 34% of the patients. GI bleed was significantly higher in DSS.HESS test was positive in more DSS cases than DHF.But this is not statistically significant.

FIGURE .1

CLINICAL FEATURES

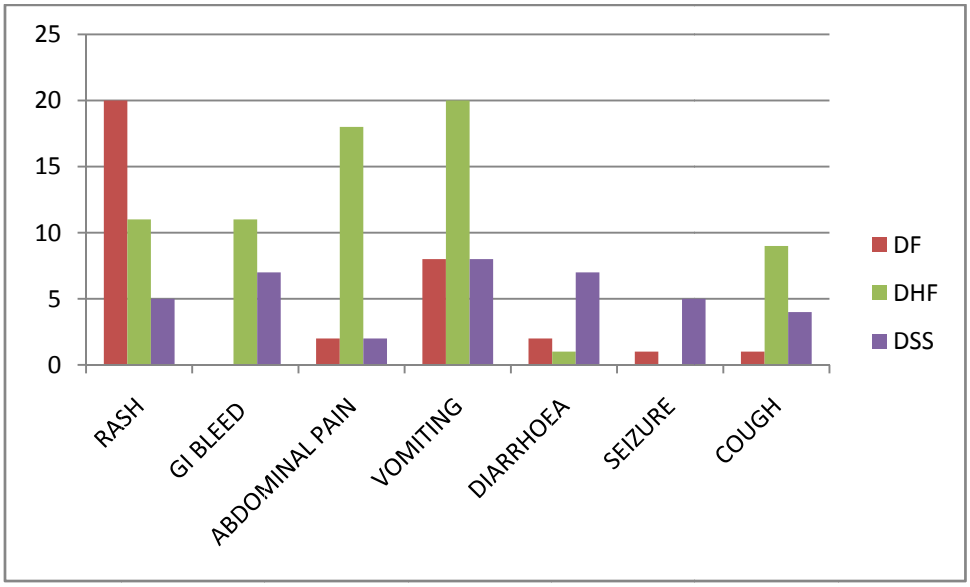


FIGURE .2

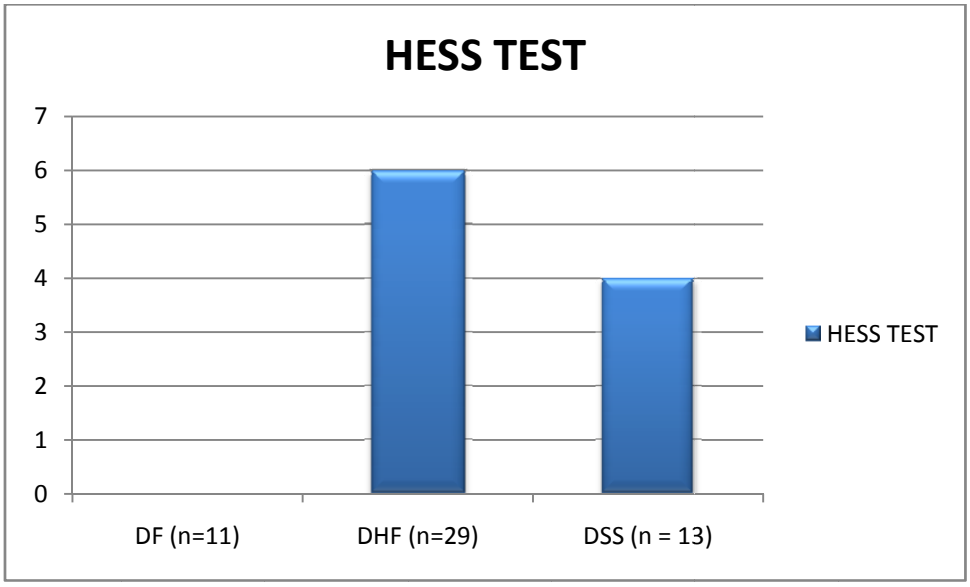
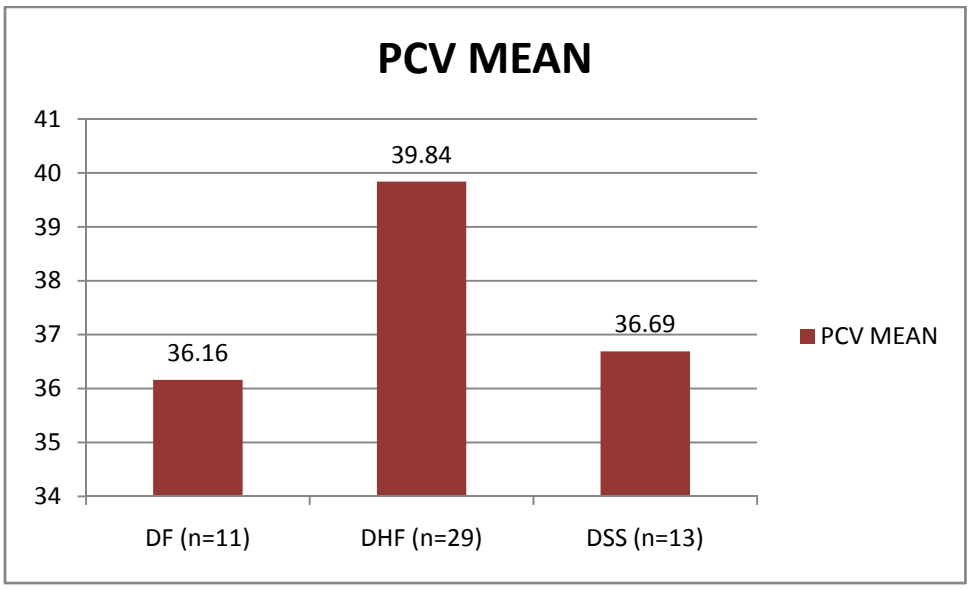


TABLE 4

HEMATOLOGICAL VALUE

No	Features	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P VALUE
1	PLATELET COUNT mean(SD)	70132 (±53684)	89636 (±55352)	71206 (±59996)	51230 (±28249)	0.2
2	PCV mean(SD)	38.30 (±6.10)	36.16 (±4.95)	39.84 (±6.54)	36.69 (±5.35)	0.12



The mean platelet count was 70132.DSS cases had a lower count than the mean. but it is not statistically significant . Mean hematocrit value was comparatively higher in DHF. But it was not statistacally significant.

TABLE 4

PLATELET COUNT (Per cu mm)

NO	PLATELET COUNT	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P
1	<20000	2(3.8%)	0	1(3.4%)	1(7.7%)	0.21
2	20000-50000	21(39.6%)	3(27.3%)	13(44.8%)	5(38.5%)	
3	50001-100000	20(37.7%)	6(54.5%)	7(24.1%)	7(53.8%)	
4	>100000	10(18.9%)	2(18.2%)	8(27.6%)	0	

Most patients had a platelet count between 20,000-50,000(39.6%).While DHF patients commonly had counts less than 50,000 ,the counts were more than 50,000 in 53.8% of DSS cases. But this is not statistically significant.

TABLE 5

SGOT&SGPT>50IU

No	Features	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P VALUE
1	SGOT (%)	48(90.6%)	10(90.9%)	26(89.7%)	12(92.3%)	0.9
2	SGPT (%)	46(86.8%)	9(81.8%)	26(89.7%)	11(84.6%)	0.7

SGOT and SGPT values were increased in all the groups. But this is not statistically significant.

FIGURE 3

SGOT&SGPT

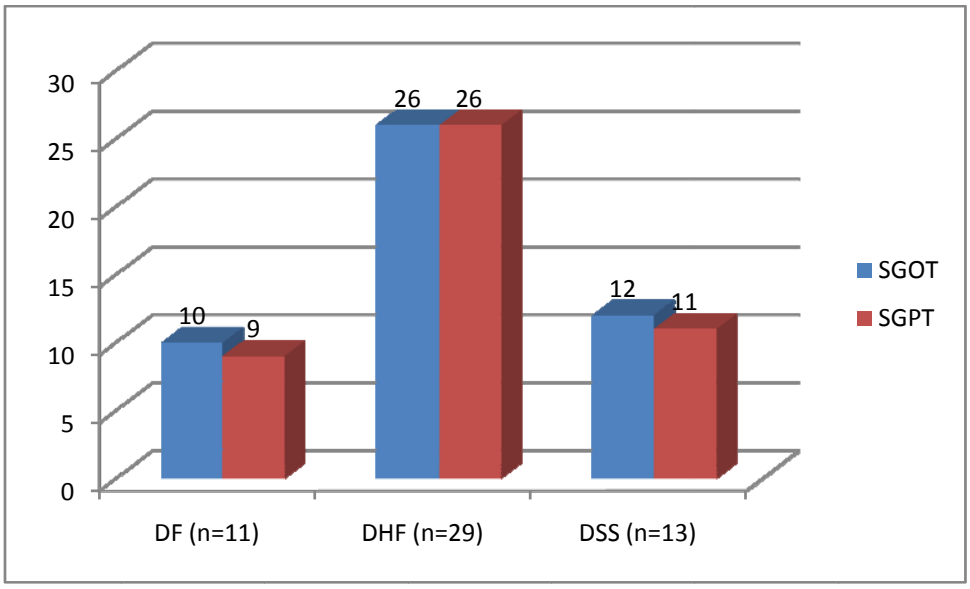


TABLE 6

ULTRA SOUND FINDINGS

No	Features	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P VALUE
1	HEPATOMEGALY	20 (37.7%)	8 (72.7%)	8 (27.6%)	4 (30.8%)	0.001
2	RIGHT PLEURAL EFFUSION AND ASCITES	25 (47.2%)	0	20 (69%)	5 (38.5%)	0.001

Hepatomegaly is a significant finding in all groups. 69%DHF cases had polyserositis. It is statistically significant.

FIGURE 4

USG FINDINGS

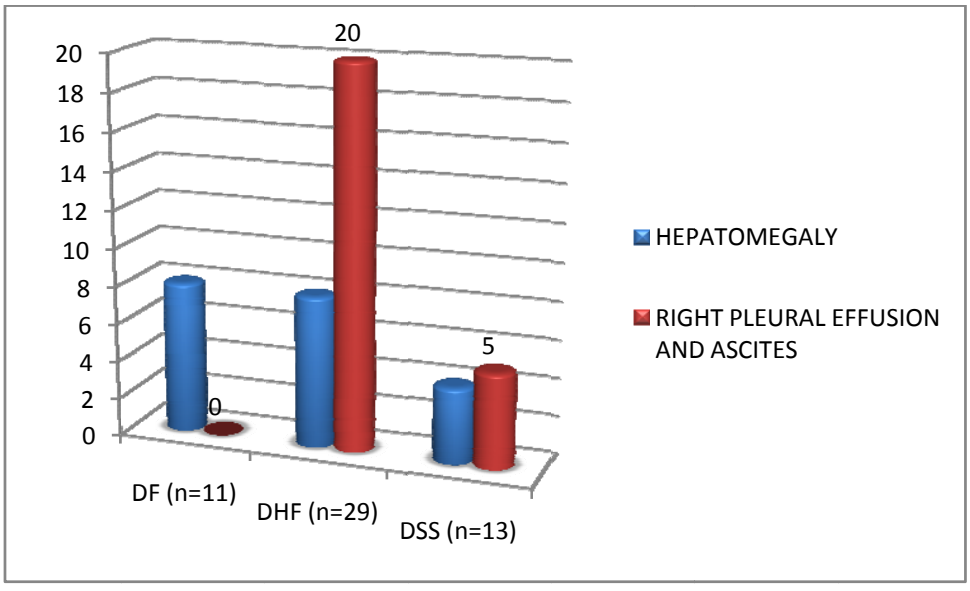


TABLE 7

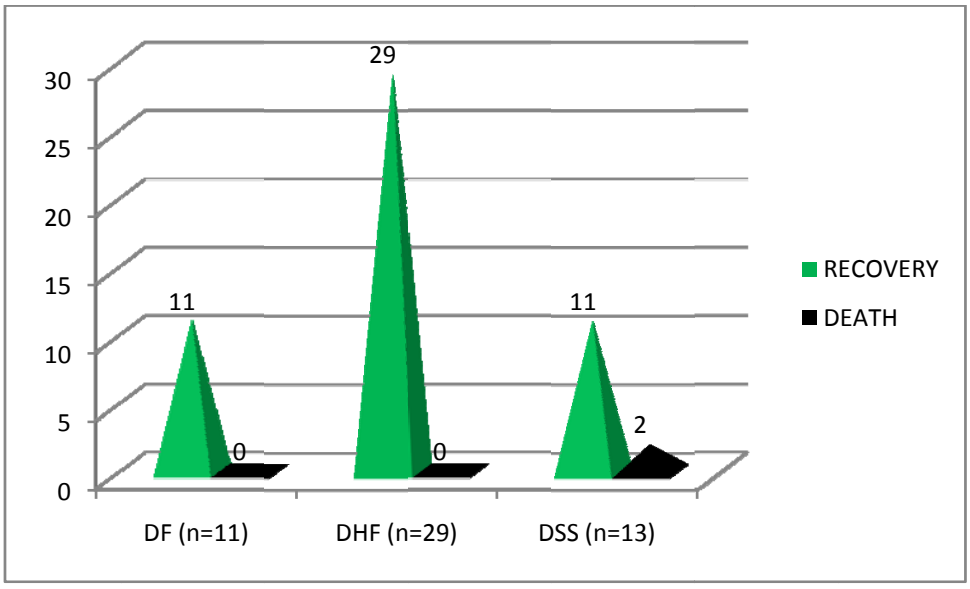
OUTCOME

No	Features	TOTAL (n=53)	DF (n=11)	DHF (n=29)	DSS (n=13)	P VALUE
1	RECOVERY (%)	51(96.2%)	11(100%)	29(100%)	11(84.6%)	0.04
2	DEATH(%)	2(3.8%)	0	0	2(15.4%)	0.04

2 cases of DSS(CFR-3.5%) from the entire study group died. DF&DHF had a complete recovery.

FIGURE 5

OUT COME



DISCUSSION

As discussed in the literature, SouthEastAsian region has a varied clinical profile and outcome compared to the rest of the world. The demographic pattern and the trend of illness are vastly changing every year through the past decade. South India and especially SouthTamilnadu has witnessed several dengue epidemic outbreaks during the past few years. Here I compare the clinical profile and outcome of Dengue in our hospital with other Indian and study done other countries.

Totally 53 Sero-positive cases dengue children who presented at Tirunelveli Medical College hospital during the study period were analysed. As per the WHO classification, the frequency of Dengue fever was 20.8%, Dengue hemorrhagic fever 54.7% and Dengue shock syndrome 24.5%, while no cases presented Dengue fever having unusual bleed.(i.e. bleeding without plasma leakage) Narayanan et al (Chennai2001)reported DF (72.78%), DHF (18.6%), DSS (8.4%). Kalyanarooj et al (Indonesia) reported DF (including DFB) (53%), DHF (including DSS)(47%). Ratageri et al(Hubli2003) reported DF(18%),DHF (includingDSS) is 82%. In present study, DHF (including DSS) is 79.2%. Present study is comparable with other studies.

This shows that severe forms of dengue-DHF and DSS have increased over the decade. It may be due to increasing endemicity, environmental factors and changing virulence of the viruses.

Baseline microvascular permeability in children is greater than that of adults and this could partly explain why DHF and DSS are more frequently seen in children[38].

AGE:

In the present study Dengue infection was noted in 17% of infants , 1-5yrs(20.8%)and 62.3% of children 6-12yrs was observed. Manjunath J. Kulkarni et al Clinico-Epidemiological Profile of Children Hospitalized with Dengue Indian J Pediatr (2010) 77:1103–1104 study shows Children in 6–12 yrs age group constituted 45.8% of cases forming the most commonly affected group. Fahad Javaid Siddiqui et al. Study shows older children appeared 5.5 times more likely to be affected than their younger (0 – 5 years) counterparts. These are comparable with our present study.

SEX:

In the present study, there is no sex predilection for the disease (male 49.1% compared to female 50.1%), while both sexes had equal distribution of disease severity. Regarding the relationship between gender and severity among children, Nimmannitya(1987a,b) reported that shock and death occurred more frequently in females than in males. (Garcia-Rivera *et al,* 2003;. studies reporting no significant difference in frequency between male and female.

FEVER:

In the present study all children had fever. Mean duration fever was 6.02 days. In DSS mean duration of fever was 5.14 days. Chandrakanta,et al study shows mean duration of fever 10.7%.

VOMITING:

In the present study 67.9% children had vomiting. Manjunath J. Kulkarni et al reported vomiting in 35.2% children.Chandrakanta,et al (Changing clinical manifestations of dengue infection in north India dengue bulletin 2008)shows vomiting was 41.2%. Ratagiri et al study shows 82%.The percentage is variable in different studies.

ABDOMINAL PAIN:

In the present study 41.5% children had abdominal pain. Chandrakanta,et al study shows 25%.Shigeki Hanafusa et al study shows 68%.In the present study abdominal pain was significantly more common in DHF (62.1%).

GI BLEEDING:

The present study shows 34% incidence of GI bleeding. Chandrakanta,et al shows 38.8%. Narayanan et al shows high percentage 61% of hematemesis. In the present study GI bleeding was significantly more common in DSS.

SHOCK

No	Study	%
1	Aggarwal et al	33
2	Gomber et al	20
3	Narayanan et al	8.4
4	Kabilan et al	23.8
5	Ratagiri et al	22
6	Present study	24.5

DSS was low in Narayanan et al. Due to increasing endemicity and changing epidemiology, DSS is in increasing trend.

RASH:

Chandrakanta, et al study shows 37.5% cases had skin rash. Shigeki Hanafusa1,2.et al SOUTHEAST ASIAN J TROP MED PUBLIC HEALTH Vol 39 No. 2 March 2008 study shows 55.1%. In the present study shows 37.7% of skin rash. It is comparable with other studies.

TOURNIQUET TEST:

In the Present study shows 18.9% positivity. Shigeki Hanafusa (Japan) et al study shows 85.7%tourniquet test positive. 23.7% in Narayanan and 52% in Kalyanarooj (Indonesia).The low percentage in our study(similar to another Indian study narayanan et al)compared to foreign studies may be due to difference in skin complexion and capillary fragility in Indian children.

DIARRHOEA:

Chandrakanta, et al study shows 6.2% of children had loose stools. In the present study 18.9% children had diarrhea and is statistically significantly reported in DSS cases .This may be due to the poor socio economic status and nutritional status in our children,predisposing to early shock in dengue.

SEIZURE:

Chandrakanta et al study shows 45% cases had seizure. In present study 11.3% cases had seizure.Most of the seizure occurred in DSS 38.5% .

COUGH:

Shigeki Hanafusa et al study shows 35.4% children had cough. Manjunath J. Kulkarni study shows 9.07% . In the present study 26.4% of children had cough. Cough is a **Unique** feature of paediatric dengue compared to adult dengue.

MEAN HEMATOCRIT:

Chandrakanta, et al study shows mean hematocrit value 26.8 %. Narayanan et al study shows 33.2%. Karthis et al study shows 34.06%. In the present study, mean hematocrit value is 38.30%.

PLATELET COUNT:

In present study platelet count is as follows

<20000=3.8%

20000-50000=39.6%

50001-100000=37.7%

>100000 =18.9%

Maimoona M. Ahmed J Infect Dev Ctries 2010; 4(8):503-510.study showed

<20000=6.75%

20000-50000=50%

50001-10000=41%

>100000=18.5%

Present study is comparable with this study.

In the present study, there is no correlation between the counts and the disease severity with 48.2% of DHF occurring in children with counts less than 50,000 while 53.8% of DSS in children with counts more than 50,000.this is because in dengue, the Development of antibodies potentially cross-reactive to plasminogen could have a role in causing haemorrhage[39]. The increased destruction or decreased production of platelets could result in thrombocytopenia.count may thus not necessarily correlate to bleeding or disease severity.

SGOT&SGPT:

Maimoona M. Ahmed study shows elevated liver enzyme value. Sharma et al. from India[40] reported elevated transaminases in 90% of patients In the present Study SGOT is elevated in 90.6% of the cases. SGPT is elevated in 86.8% of the cases. In the present study serum Amylase level elevated .It was

72.7%,65.5%,69.2% in DF,DHF,DSS respectively. But it was statistically not significant.

USG ABDOMEN:

Srikiatkhachom(Indonesia) study shows hepatomegaly 56% . Venkatasai study also had 21% of hepatomegaly. In present study there was hepatomegaly 37.7% of patient .It was statistically significant.

The present study shows statistically significant right side pleural effusion and ascites, which is consistent with the pathophysiology of the plasma leakage in dengue.

MORTALITY

Kabra et al study shows 12-13% of mortality.Agarwal et al study shows 6% of death .4.8% of mortality in gomberstudy. The present study shows 3.8% of mortality which is consistent with the WHO observed case fatality rates in india(3-5%).The higher rates could be due to the higher rural population that reports to our institution.

LIMITATIONS OF THE STUDY

1. Confirmation of dengue viral infection was not done. So, all the cases in the study are PROBABLE DENGUE according to WHO case definition.
2. Viral antibody titers were not done to diagnose primary and secondary dengue precisely .Only qualitative IgM was done .quantitative analysis and IgG titre analysis could not be done.
3. Serotypes were not done. So the predominant serotype was not identified.
4. Treatment modalities like type of fluid used, need for inotrope support, ventilator support, need for blood products were not studied.

CONCLUSION

1. Dengue fever is becoming more prevalent in India, especially south India. Incidence of Dengue shock syndrome is increasing.
2. Children between 6 and 12 yrs were most affected by dengue in my study.
3. There was no sex predilection.
4. Abdominal pain is a significant symptom in children with bleed(DHF).it is not a symptom to be ignored .Abdominal Pain in a child with suspected dengue should alert us to the possibility of GI bleed.
5. Cases initially diagnosed as acute watery diarrhoea, eventually turned out to be dengue. And diarrhoea children with suspected dengue were significantly prone for DSS. Hence, high index of suspicion and aggressive management are the need in such cases.
6. Seizure was significant in DSS cases. Any dengue child throwing convulsions should hence be promptly evaluated for unrecognised shock.
7. The bleeding in dengue is not purely due to thrombocytopenia. It is due to multiple etiologies including vascular changes. Refraining from treating the platelet numbers rather than the patient and strict adherence to protocols would go a long way in preventing iatrogenic complications like fluid overload.
8. There is no role for prophylactic platelet transfusion.

9. Children who presented to our setup with bleed significantly progressed to DSS. It is thus an alarming sign.
10. Early recognition, precise assessment and appropriate treatment as per established WHO protocols should reduce the high mortality rates.
11. There is a probable need for region specific guidelines for better outcomes.

PROFORMA FOR DENGUE FEVER

Name : I.P.No: Age / Sex :

Blood group :

Address : Ad. on Discharge

Fever : Type

Duration

Ass.with chills and rigor

Previous Antibiotic Therapy & Duration

Cough / Rhinitis :

Vomiting :

Hemetemesis

Malena

Hematuria

Diarrhoea

Abdominal pain

Breathing Difficulty : Headache / Eye pain / back pain. Myalgia / Arthralgia / Neck pain. Facial puffiness / Eyelid edema /Throat pain / Ab. distension / Altered sensoriam / Irritable cry / Refusal of feeding

Maculo papularash / Petechial

Seizure

General Examination

Periphries Cold / Warm PR RR Temp

Febrile / Afebrile

Palar / Ictrus Hess test : BP

Lymphadenopathy

Pedal edema

Cyanosis

CVS RS P/A

CNS

INVESTIGATION

Blood Urea LFT

Sugar SGOT

Creatinine SGPT

Na + T. Protein

K + Albumin

Sr. Amylase

CBC

TC DC Hb ESR

Date					
Platelet					
PCV					

Peripheral smear

X – ray chest

USG Abdomen

Dengue Serology with date

WIDAL

Urine	Albumin	PT
	Sugar	
	Deposit	APTT

Transfusion

Treatment

Outcome: cured/expired

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S.NO	AGE	SEX	BL.GP	BL.TYP	PLACE	DOA	DOD	F. TYPE	F. DAYS	F. CHILLS	COUGH	VOMITING	HEMETEMESIS	MALENA	DIARHOEA	ABD.PAIN	OTHERS
1	10M	M	B	P	KADAYAM	03.01.10	12.01.10	LOW	10	NO	NO	NO	NO	NO	NO	NO	NO
2	10	F	AB	P	KADAYAM	05.01.10	14.01.10	HIGH	4	NO	NO	2episode	NO	NO	NO	NO	NO
3	9	F	B	P	KOVILPATTI	10.01.10	15.01.10	LOW	7	NO	4 DAYS	NO	NO	NO	NO	NO	NO
4	10	M	B	P	KADAYAM	02.01.10	10.01.10	LOW	8	NO	NO	2episode	NO	1 episode	NO	NO	NO
5	1	F	B	N	VEERAVANALLUR	11.01.10	17.01.10	LOW	5	NO	NO	NO	1episode	NO	NO	NO	NO
6	10	F	A	P	PETTAI	03.01.10	08.01.10	LOW	4	NO	NO	2episode	2episode	NO	NO	NO	breathing difficulty
7	8	M	B	P	KOVILPATTI	12.01.10	17.01.10	LOW	4	NO	NO	2episode/day 2days	1episode	1 episode	NO	NO	NO
8	10	F	B	P	KOVILPATTI	11.01.10	16.01.10	LOW	5	NO	NO	2episode/day 2days	NO	NO	NO	3 DAYS	ab distension
9	7	F	B	P	KOVILPATTI	12.01.10	16.01.10	HIGH	5	NO	NO	3-4episode/day	NO	NO	NO	2 DAYS	NO
10	8	F	A	P	SIVAGIRI	11.01.10	16.01.10	HIGH	4	NO	NO	3-4episode/day	NO	1 episode	NO	NO	NO
11	9	M	B	P	KOVILPATTI	15.01.10	21.01.10	HIGH	5	NO	NO	2episode/day 2days	NO	NO	NO	NO	NO
12	7	M	O	P	KADAYAM	10.01.10	15.01.10	HIGH	5	NO	NO	2episode/day 1day	NO	1 episode	NO	NO	NO
14	11M	M	O	P	KADAYAM	14.01.10	18.01.10	LOW	7	NO	NO	NO	NO	NO	NO	NO	NO
15	11	F	O	P	KADAYAM	10.01.10	21.01.10	LOW	7	NO	NO	3episode/day	NO	1 episode	NO	NO	NO
16	9	M	B	P	KADAYAM	15.01.10	21.01.10	LOW	5	NO	NO	3episode/day	NO	NO	NO	NO	NO
17	12	F	B	P	KADAYAM	21.01.10	25.01.10	HIGH	5	NO	NO	7episode/day-4day	NO	NO	NO	4 DAYS	NO
18	12	M	B	P	KOVILPATTI	21.01.10	26.01.10	HIGH	4	NO	NO	5episode/day	2episode	1 episode	4-5episode/day	NO	1epistaxis
19	8M	F	B	P	KADAYAM	17.01.10	21.01.10	HIGH	8	NO	2 DAYS	NO	NO	NO	NO	NO	breathing difficulty
20	4	F	B	P	KADAYAM	21.01.10	27.01.10	HIGH	2	NO	NO	3episode/day	NO	NO	5-6episode/day	NO	NO
21	8	F	B	P	KADAYAM	23.01.10	29.01.10	LOW	3	NO	NO	2-3episode	NO	NO	NO	1 DAY	NO
22	3	M	B	P	KOVILPATTI	26.01.10	02.02.10	LOW	2	NO	NO	3-4episode/day	NO	NO	NO	NO	NO
23	8	M	B	P	TIRUNELVELI	20.12.09	30.12.09	HIGH	14	NO	10 DAYS	NO	3-4episode	3 episodeS	5-6episode/day	6 DAYS	Alteredsensorium
24	9	F	O	P	KOVILPATTI	14.12.09	18.12.09	LOW	7	NO	NO	3-4episode/day	NO	NO	5-6episode/day	NO	NO
25	10	M	B	P	SANKARANKOIL	23.12.09	29.12.09	INTERM	6	NO	7 DAYS	2-3episode	NO	NO	NO	2 DAYS	NO
26	6	M	A	N	VK PUTHUR	21.12.09	25.12.09	HIGH	6	NO	NO	3-4episode/day	2episode	1 episode	NO	NO	NO
27	8	M	O	P	MARUTHAIPUTHUR	15.12.09	23.12.09	HIGH	7	NO	NO	3-4episode/day	NO	NO	NO	2 DAYS	NO
28	7M	M	O	P	THERKUPATTAI	19.12.09	31.12.09	HIGH	4	NO	NO	2days	NO	NO	2 days	NO	NO
29	11M	M	O	P	TENKASI	24.12.09	29.12.09	INTERM	5	NO	4 DAYS	3episodes	NO	NO	NO	2 DAYS	NO
30	8M	M	O	P	TIRUNELVELI	15.12.09	23.12.09	HIGH	7	NO	NO	4episodes/4days	NO	NO	NO	2 DAYS	NO
31	12	F	B	P	TIRUNELVELI	19.01.10	26.01.10	INTERM	7	NO	NO	4episodes/4days	NO	NO	NO	NO	dehydration
32	11	F	A	P	TIRUNELVELI	21.01.10	27.01.10	HIGH	6	YES	NO	2episodes	NO	NO	2 days	NO	NO
33	9M	F	O	P	KADAYAM	25.01.10	28.01.10	HIGH	7	NO	NO	2episodes	NO	NO	NO	NO	NO
34	12	M	O	P	KADAYAM	21.01.10	26.01.10	HIGH	4	NO	NO	4episodes/4days	1episode	1 episode	4-5episode/day	NO	NO
35	8M	F	B	P	SANKARANKOIL	17.01.10	21.01.10	HIGH	4	NO	NO	NO	NO	NO	NO	NO	dyspnoec,tachypnoec
36	8	F	A	P	THALYUTHU	03.01.10	08.01.10	HIGH	4	NO	NO	NO	2episodes	NO	1 day	NO	NO
37	10	F	O	P	TIRUNELVELI	03.01.10	09.01.10	HIGH	3	NO	3 DAYS	3episodes	NO	NO	4 episodes	4 DAYS	NO
38	3	M	B	P	AMBAI	11.12.09	25.12.09	INTERM	7	NO	7 DAYS	3episodes/2days	NO	NO	NO	NO	myalgia,aloc
39	4	F	B	P	TIRUNELVELI	11.03.11	18.03.11	INTERM	15	NO	NO	NO	NO	NO	NO	NO	abd dist.,facial puff.
40	4	M	B	P	TIRUNELVELI	03.12.09	12.12.09	INTERM	4	NO	NO	NO	3episodes	NO	NO	2 DAYS	NO
41	10	F	O	P	SRIVAIKUNDAM	12.12.09	18.12.09	HIGH	4	NO	NO	2-3 episodes	NO	NO	NO	2 DAYS	NO
42	8	F	B	P	KADAYAM	14.12.09	18.12.09	INTERM	7	NO	7 DAYS	5days	NO	NO	NO	5 DAYS	NO
43	3	M	B	P	KOVILPATTI	01.12.09	08.12.09	INTERM	5	NO	NO	NO	NO	NO	NO	3 DAYS	NO
44	4	F	O	P	TIRUNELVELI	08.12.09	19.12.09	HIGH	7	NO	7 DAYS	NO	NO	NO	NO	3 DAYS	NO
45	7 M	F	A	P	RAJAPALAYAM	17.12.09	22.12.09	INTERM	3	NO	4 DAYS	NO	NO	2 episodes	NO	1 DAY	NO
46	3	M	O	P	KOVILPATTI	20.12.09	27.12.09	INTERM	15	NO	10 DAYS	NO	3 episodes	NO	NO	7 DAYS	NO
47	10	M	A	P	TIRUNELVELI	23.12.09	29.12.09	INTERM	6	NO	NO	3 days	NO	NO	NO	2 DAYS	NO
48	4	M	O	P	KOVILPATTI	11.12.09	20.12.09	INTERM	7	NO	2 DAYS	NO	NO	NO	NO	2 DAYS	NO
49	10	F	O	P	TIRUNELVELI	31.01.10	07.02.10	HIGH	5	NO	NO	5 days	NO	1 episode	NO	NO	oliguria
50	11	M	O	P	TIRUNELVELI	07.04.10	10.04.10	INTERM	7	NO	NO	NO	NO	NO	NO	NO	NO
51	10	F	AB	P	RAJAPALAYAM	06.10.11	16.10.11	HIGH	6	NO	NO	3 days	NO	NO	NO	3 DAYS	NO
52	8	M	B	P	KOVILPATTI	22.03.10	03.04.10	INTERM	8	NO	4 DAYS	3 days	2 episodes	1 episode	NO	3 DAYS	NO
53	5	F	B	P	AMBAI	01.11.10	10.11.10	HIGH	10	NO	3 DAYS	NO	NO	1 episode	NO	3 DAYS	NO

S.NO	SEIZURES	PERIPHER	FEVER	PALLOR	L.PATHY	P.EDEMA	TORNIQUE	RASH	PR	RR	SYS BP	DIAS BP	UREA	SUGAR	CREAT.	NA	K	BIL.TOT	BIL.DIR	BIL.IND	SGOT	SGPT	TOT.PROT
1	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	126	60	100	70	19	97	1.2	140	4.5	1	0.7	0.3	130	160	7.2
2	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	PRESENT	112	30	90	60	19	111	1.2	138	4.9	0.7	0.5	0.2	88	40	7
3	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	100	24	100	70	15	90	0.6	140	3.8	0.9	0.5	0.4	596	138	6.8
4	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	102	22	100	70	47	91	1	138	4	0.5	0.3	0.2	32	17	7
5	NO	WARM	NO FEV	NO	NO	NO	POSITIVE	PRESENT	100	24	90	60	25	65	0.7	144	4.4	0.6	0.3	0.3	20	18	7
6	NO	COLD	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	90	46	90	60	18	68	1.2	137	4.2	0.8	0.4	0.4	73	31	5.7
7	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	PRESENT	110	26	90	60	38	71	1	134	4	1.2	0.9	0.3	883	340	6.8
8	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	110	28	100	60	40	15	0.8	144	4.2	1	0.5	0.5	339	185	7.5
9	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	136	34	100	70	15	66	0.5	122	4.1	0.9	0.4	0.5	180	100	7
10	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	130	26	100	80	15	92	0.7	137	4.4	0.8	0.4	0.4	110	80	7.4
11	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	110	24	110	70	28	86	0.8	138	3.6	0.8	0.4	0.4	148	118	7.2
12	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	116	26	90	70	15	119	0.7	136	4	0.9	0.6	0.3	23	33	6.8
14	YES	COLD	NO FEV	NO	NO	NO	POSITIVE	PRESENT	150	54	NR	NR	67	72	0.8	140	4	1	0.6	0.4	370	190	6
15	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	PRESENT	110	32	100	70	20	67	0.8	136	3.7	1.2	0.6	0.6	616	46	6.5
16	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	120	30	100	70	28	86	0.8	138	3.6	0.8	0.4	0.4	148	118	6.2
17	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	110	30	110	70	27	88	1.1	135	4.8	1.2	0.8	0.4	216	72	7.2
18	NO	COLD	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	150	32	90	60	51	60	1.1	141	4	1.2	0.6	0.6	116	67	7
19	YES	WARM	FEVER	NO	NO	NO	NEGATIVE	PRESENT	140	62	90	60	27	80	1.1	138	4	1.4	0.6	0.8	110	140	6.8
20	YES	WARM	FEVER	NO	NO	NO	NEGATIVE	PRESENT	160	30	90	60	24	62	1	138	3.8	1	0.4	0.6	100	140	7
21	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	100	24	100	70	26	118	0.8	142	4.2	0.8	0.4	0.4	145	55	7.3
22	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	PRESENT	106	32	90	70	18	94	0.7	139	4.3	1.4	0.8	0.6	108	70	6.8
23	NO	COLD	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	140	60	NR	NR	19	309	0.8	140	4.1	1.8	1	0.8	110	80	7
24	NO	WARM	NO FEV	NO	NO	NO	POSITIVE	PRESENT	96	24	100	70	20	68	0.6	140	4	1	0.6	0.4	90	70	7.2
25	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	100	30	100	70	17	114	0.9	141	4.2	0.7	0.4	0.3	126	50	5
26	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	PRESENT	96	20	96	68	18	82	0.7	138	3.6	1.2	0.8	0.6	58	48	6.8
27	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	90	20	100	70	21	96	0.8	135	4	1.4	0.7	0.7	110	130	7.2
28	YES	COLD	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	170	60	94	60	119	90	1.2	139	4.1	1	0.6	0.4	98	160	6.4
29	NO	WARM	NO FEV	NO	NO	NO	POSITIVE	PRESENT	99	20	100	70	23	99	0.8	136	4.2	1.5	1	0.5	176	100	6.9
30	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	90	20	100	70	21	96	0.8	135	4	1.4	0.7	0.7	110	130	7.2
31	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	70	15	90	60	21	76	1.2	145	4	1	0.8	0.2	110	140	8
32	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	96	26	100	70	21	96	1.2	136	4	1	0.8	0.2	110	120	8
33	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	87	23	98	76	18	98	1.2	145	5	1	0.8	0.2	107	114	7.5
34	NO	COLD	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	98	20	98	76	51	60	1.1	141	4	1.2	0.6	0.6	116	67	8
35	YES	COLD	FEVER	NO	NO	NO	POSITIVE	PRESENT	110	62	70	40	27	60	1.2	138	4	1.4	0.4	1	110	140	6.4
36	NO	COLD	FEVER	YES	NO	YES	NEGATIVE	ABSENT	110	80	90	70	23	70	1.6	140	5	1.2	0.8	0.4	115	136	6
37	NO	COLD	FEVER	YES	NO	NO	NEGATIVE	ABSENT	120	21	100	70	23	96	1.3	145	5.3	1.6	0.8	0.8	110	200	7.6
38	YES	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	170	40	100	60	88	99	1	140	4.2	0.6	0.4	0.2	110	150	6.1
39	NO	WARM	FEVER	NO	NO	YES	NEGATIVE	ABSENT	130	36	110	70	16	71	1	140	3.7	0.5	0.3	0.2	34	24	6.7
40	NO	WARM	FEVER	YES	NO	NO	NEGATIVE	PRESENT	120	22	90	70	30	70	1	140	4	1	0.8	0.2	110	120	8
41	NO	WARM	FEVER	NO	NO	NO	POSITIVE	PRESENT	110	24	100	70	25	68	0.8	140	4	1.4	0.9	0.5	118	100	6.2
42	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	110	28	100	80	28	70	1	138	4.3	1.2	0.8	0.4	130	90	6.8
43	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	100	28	90	70	45	69	0.8	147	4.7	1.1	0.6	0.5	150	100	7
44	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	PRESENT	120	30	90	70	33	90	0.9	138	4.2	1.2	0.8	0.4	170	120	7.2
45	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	120	36	80	60	19	75	0.6	136	4.5	1	0.4	0.6	90	80	6.8
46	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	100	30	90	70	18	64	0.6	140	4.5	1	0.7	0.3	2076	724	5.8
47	NO	WARM	FEVER	NO	NO	NO	POSITIVE	PRESENT	110	24	100	70	24	70	0.9	140	3.6	1.1	0.5	0.6	90	140	6.8
48	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	100	30	90	70	24	58	0.8	134	3.7	1.4	0.8	0.6	78	110	7
49	NO	COLD	NO FEV	YES	NO	NO	POSITIVE	PRESENT	140	40	100	70	56	62	1	140	3.2	2.3	1.5	1	10	15	5.1
50	NO	WARM	NO FEV	NO	NO	NO	NEGATIVE	ABSENT	90	24	110	70	30	70	1.4	140	3.6	1	0.5	0.5	160	140	6.4
51	NO	WARM	FEVER	NO	NO	NO	POSITIVE	PRESENT	110	26	100	70	25	125	0.9	131	3.4	1.4	0.4	1	180	260	7.4
52	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	ABSENT	110	28	100	70	20	78	0.8	140	4.3	1	0.4	0.6	350	300	7
53	NO	WARM	FEVER	NO	NO	NO	NEGATIVE	PRESENT	120	24	100	76	26	100	1	138	3.6	1.2	0.6	0.6	340	320	7.4

S.NO	ALBUMIN	AMYLASE	TC	DCP	DCL	DCE	HB	ESR30	ESR60	PLATELET	PCV	X RAY CHEST	USG ABDOMEN	U.ALB	U.SUG	U.DEP	U.CS	B.TRANSFUSION	DENG.CAT	OUTCOME
1	4.2	190	16700	55	45	0	11.7	10	22	180000	36	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
2	4.4	108	4000	50	50	0	10.8	14	24	70000	30	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	1 PLATELET	DF	RECOVERY
3	4	88	5200	45	52	3	14.3	2	5	43000	44	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
4	4	208	9600	92	5	3	11.6	30	62	100000	33	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
5	3.5	180	4500	27	70	3	15	2	7	23000	47	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	1 PLATELET	DHS	RECOVERY
6	3.7	60	8800	31	56	13	12.6	18	67	62000	37	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DSS	RECOVERY
7	4	78	4200	40	60	0	13.1	4	10	36000	41	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	3 PLATELET	DF	RECOVERY
8	4.5	90	5800	32	68	0	12.3	10	25	78000	38	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
9	4	110	25000	53	40	7	10.9	8	20	34000	37	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
10	4.4	70	6300	34	63	3	11	5	12	35000	40	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
11	4.2	90	6500	27	56	17	11	5	10	101000	43	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
12	4.3	60	5500	42	58	0	14.7	4	9	32000	46	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	2 PLATELET	DHS	RECOVERY
14	3.5	80	7000	52	44	4	11	10	18	90000	40	R PF	HEPATOMEGALY	NEG	NEG	NIL	NIL	3 UFFP	DSS	DEATH
15	3.6	94	6000	40	60	0	12	12	24	63000	30	R PF	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
16	3.8	110	8000	38	60	2	12	10	20	110000	43	R PF	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
17	4	150	7000	32	66	2	10	8	20	41000	48	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
18	4	114	5000	42	54	4	14.2	20	36	55000	41	NORMAL	NORMAL	NEG	NEG	NIL	NIL	1UBlood	DSS	RECOVERY
19	3.8	120	21000	33	63	4	11	10	20	23000	33	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	2 PLATELET	DSS	DEATH
20	4	110	10000	33	64	3	12	8	18	40000	33	PNEUMONIA	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
21	4.3	140	6200	30	70	0	11	6	14	28000	51	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	1 PLATELET	DHS	RECOVERY
22	3.8	90	5400	34	62	4	10	12	24	90000	40	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
23	4	160	9000	45	55	0	10.5	1	10	20000	31	R PF	R PF ASCITES	TRACE	NEG	NIL	NIL	1uFFP&3uPLATELET	DSS	RECOVERY
24	4.2	150	5400	25	70	5	11.8	10	22	76000	36	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
25	2.3	210	10700	50	42	8	12.2	2	6	23000	36	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	1 PLATELET	DF	RECOVERY
26	3.8	120	3400	24	72	4	12	15	32	103000	37	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
27	4.2	120	3500	46	52	2	14.4	1	4	254000	44	NORMAL	R PF ASCITES	NEG	POS	NIL	NIL	NIL	DHS	RECOVERY
28	3.3	130	5200	49	49	2	10.7	2	4	26000	33	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	3 PLATELET	DSS	RECOVERY
29	4.1	110	7000	47	52	1	14	1	3	28000	44	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
30	4.2	120	5400	22	74	4	14.4	1	4	254000	44	R PF	R PF ASCITES	NEG	POS	NIL	NIL	NIL	DHS	RECOVERY
31	5	100	5200	49	49	2	14	1	3	89000	41	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
32	4	100	7200	39	60	1	16	1	3	85000	41	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
33	4	100	6700	21	78	1	14	1	3	200000	40	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
34	5	112	5800	34	65	1	14.7	1	2	55000	41	NORMAL	NORMAL	NEG	NEG	NIL	NIL	1u whole blood	DSS	RECOVERY
35	3.1	150	2800	60	37	3	14	1	4	23000	33	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DSS	RECOVERY
36	4	102	20400	78	20	2	14	1	3	62000	37	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DSS	RECOVERY
37	4.3	100	5000	70	26	4	12	1	4	93000	35	NORMAL	NORMAL	NEG	NEG	NIL	NIL	NIL	DSS	RECOVERY
38	3.1	112	5400	73	24	3	14.2	5	12	95000	44	PNEUMONIA	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DSS	RECOVERY
39	3	37	6600	41	53	6	7.5	8	16	80000	26	PNEUMONIA	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
40	5	110	4800	33	65	2	7	5	8	24000	23	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	1 UFFP	DHS	RECOVERY
41	3.2	100	6100	23	75	2	15.7	5	12	22000	47	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	1 PLATELET	DHS	RECOVERY
42	3.8	104	7000	20	80	0	12	10	20	76000	37	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
43	4	110	4100	50	48	2	11	22	30	93000	34	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DF	RECOVERY
44	4.2	140	5200	32	66	2	10	10	20	34000	36	R PF	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
45	3.8	90	6600	17	80	3	10	14	20	58000	32	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
46	2	220	15000	70	24	6	9.3	20	30	112000	28	PNEUMONIA	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
47	3.8	98	5000	36	60	4	10	12	20	23000	36	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	1 PLATELET	DHS	RECOVERY
48	3.8	70	3000	30	68	2	11.2	4	8	95000	44	PNEUMONIA	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
49	3.1	40	14000	40	45	15	9	30	40	23000	27	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	2u platelet	DSS	RECOVERY
50	3.4	123	5100	33	65	2	11.4	5	12	114000	36	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
51	4.2	32	3600	50	46	4	14.8	1	3	20000	45	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	1 PLATELET	DHS	RECOVERY
52	4	180	8000	40	58	2	11	10	14	60000	39	NORMAL	HEPATOMEGALY	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY
53	4.2	160	12500	39	57	4	14.3	3	10	24000	48	NORMAL	R PF ASCITES	NEG	NEG	NIL	NIL	NIL	DHS	RECOVERY