CHAPTER

3

Management of Dengue

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INTRODUCTION

Dengue is the world's most common mosquito-borne viral infection and a leading cause of morbidity throughout the tropics and subtropics.[1] Each year, there are about 50-100 million dengue infections and about 5,00,000 individuals hospitalized with DHF, mainly in Southeast Asia.[2]

Globally, dengue virus transmission has expanded in recent years, and all four dengue virus serotypes are now circulating in Asia, Africa, and the Americas, representing a global pandemic.[3] Approximately 70% of the population at risk for dengue worldwide lives in the WHO south east Asian region and western Pacific region, which bear nearly 75% of the current global disease burden due to dengue.[4]

Dengue epidemiology in India has dramatically changed over the last few decades. After the first major nationwide outbreak of DHF in the year 1996, gradual dengue virus expansion started in the entire nation. A steady increase in the number and frequency of outbreaks has followed, and, at present, in most of the states of India, all four serotypes are prevalent.[5]

EPIDEMIOLOGY[6]

The epidemiology of dengue depends upon a complex relationship between epidemiological factors, viz. host (man and mosquito), agent (virus) and the environment.

Dengue Virus

Dengue virus belongs to the genus Flavivirus in the family Flaviviridae. It is a positive-stranded encapsulated ribonucleic acid (RNA) virus composed of three structural protein genes that encode the nucleocapsid or core protein, a membrane-associated protein, an enveloped glycoprotein, and seven nonstructural proteins.

There are four antigenetically related but distinct serotypes of the dengue virus: DENV-1, DENV-2, DENV-3, and DENV-4. Each serotype has several genotypes. DENV-1 has three, DENV-2 has two, and DENV-3 and DENV-4 each have four. In humans, one serotype produces lifelong immunity against reinfection but only temporary and partial immunity against the other serotypes. Each serotype has unique characteristics and can present with severe manifestations in a particular population depending upon its interaction with the host response.

Host

People of all ages and both genders are at risk of being infected. Travel to dengue endemic areas is a very important risk factor in transmission of disease- it is the commonest cause of fever in the travelers returning from these areas, overtaking malaria and typhoid.

Dengue is transmitted from an infected person to others by the bite of the female Aedes aegypti mosquito (main urban vector) and the Aedes albopictus mosquito. Though transmission primarily occurs through the bite of a vector, there are reports of transmission through blood transfusion,[7] organ transplantation[8] and vertical transmission.[9]

Environment

Ae.aegypti breeds in domestic man-made water receptacles whereas Ae.albopictus prefers natural larval habitats. Seasonal variation in dengue transmission is due to the survival characteristics of vectors, best between 16-30°C at relative humidity of 60-80%.

CLINICAL FEATURES

Dengue viruses cause symptomatic infections or asymptomatic seroconversion. Symptomatic dengue infection is a systemic and dynamic disease. It has a wide clinical spectrum that includes both severe and non-severe clinical manifestations. After the incubation period of 4 to 7 days, it is followed by three phases – febrile, critical and recovery.[6,10]

Febrile phase: Onset of DF with sudden rise in temperature, lasts for around 4-5 days and is usually associated with severe frontal headache, myalgia, retro-orbital pain, flushing and rash. Rash may be maculopapular or scarlatiniform, usually appears after 3rd/ 4th day of fever. A second episode of fever and symptoms can arise, called "saddleback" pattern. Atypical features are enumerated in Table 1.

Potential complications can include

- Dehydration due to decreased fluid intake, emesis, and increased metabolic state.
- Febrile convulsions

Critical phase (Leakage phase): Occurs after 3-4 days after onset of fever. It is characterized by hypovolemia and hemorrhagic manifestations due to increased vascular permeability and plasma leakage, which persists for 36-48 hours.

Potential complications can include[11]

- Unrecognized plasma leakage/ hemorrhage leading to shock.

Table 1: Atypical clinical presentations of Dengue

System	Clinical presentation
Respiratory system	ARDS, pulmonary oedema, pulmonary hemorrhage[12,13]
Cardiac system	Myocarditis,[14] arrhythmias, pericardial effusion[15]
Neurological system	Encephalitis,[16] encephalopathy, intracranial hemorrhage,[17] Guillan-Barre syndrome,[18] febrile seizures[19]
Gastrointestinal system	Acalculous cholecystitis,[20] Febrile diarrhea,[21] Hepatitis/Fulminant hepatic failure,[22] acute pancreatitis,[23] bleed from pre-existing peptic ulcers,[24] spontaneous splenic rupture[25]
Renal system	Acute renal failure, acute tubular necrosis,[26] hemolytic uremic syndrome, metabolic abnormalities[27]

- Pleural effusion

Convalescent phase (Recovery phase): Usually occurs after 6-7 days of fever and lasts for 2-3 days. ECF lost during capillary leakage returns to circulatory system. Clinical improvement is seen.

Potential complications can include

- Intravascular fluid overload due to continual aggressive volume resuscitation during convalescence.

Differentiating Dengue from other febrile illnesses (OFIs) (Table 2):

India, like most developing countries have epidemics of febrile illnesses that can be confused with DF.

At presentation, DF and other febrile illnesses may share similar clinical features, including headache, myalgia, and rash.[28] Early distinction between dengue and OFI would help clinicians to identify patients who should be closely monitored for signs of DHF and stratify them accordingly.

Differences in clinical and laboratory features between dengue and other febrile illnesses have been reported; however, published studies vary considerably in terms of the parameters used, which impacts the clinical applicability of these differences.

A diagnostic accuracy study done in Brazil showed that conjunctival redness and decreased leukocyte count were independent predictors of DF.[29]

Table 2: Differential Diagnosis of Other Febrile Illness

OFI	Feature
Malaria[32] Enteric fever[33]	Fever with rigors and presence of Splenomegaly
Influenza[34]	Presence of Upper respiratory tract symptoms
Leptospirosis[35]	Progressive jaundice more often in leptospirosis.
Sepsis and Meningococcal infection[36]	Shock will coincide with high temperatures in sepsis. Dengue-shock usually occurs after defervescence, and will have clinical-radiological signs of plasma leakage.
Chikungunya Fever[37]	Symmetric arthritis of small joints pathognomic of chikungunya.
Scrub Typhus[38]	Presence of eschar in typhus. Bleeding uncommon in patients of typhus.
Viral Exanthems[39]	Rash distribution: Measles,Rubella-from head to trunk and extremities. Dengue-Trunk to face and extremities
Acute acalculous cholecystitis/appendicitis[40]	Gall bladder edema on USG due to plasma leakage in dengue, as compared to inflammation in cholecystitis/ appendicitis.
Primary HIV infection[41]	Generalised adenopathy and lack of signs of plasma leakage

A systematic review of literature published by NIH showed that patients with dengue had significantly lower platelet, white blood cell and neutrophil counts, and a higher frequency of petechiae than OFI patients. Higher frequencies of myalgia, rash, hemorrhagic signs, lethargy/prostration, and arthralgia/joint pain and higher hematocrits were reported in adult patients with dengue but not in children.[28]

More prospective studies are needed to construct a valid and generalizable algorithm to guide the differential diagnosis of dengue in endemic countries.

APPROACH TO DENGUE

1. Assessment:

a. History

b. Examination

Table 3: Classification of Dengue Fever

	Symptoms	Laboratory
DF	Fever of 2-7 days with 2 or more of the following: • Headache • Retro-orbital pain • Myalgia • Arthralgia	Leucopenia, Thrombocytopenia No evidence of plasma leakage
DHF I	DF features + Positive Tourniquet testand evidence of plasma leakage	Platelet count < 1,00,000 /cu.mm + Haematocrit rise > 20% over baseline
DHF II	DF + evidence of spontaneous bleeding and abdominal pain	Platelet count < 1,00,000 /cu.mm + Haematocrit rise > 20% over baseline
DHF III (DSS)	DF + circulatory failure: weak rapid pulse, narrow pulse pressure <20 mm Hg, Hypotension, cold clammy skin, restlessness	Platelet count < 1,00,000 /cu.mm + Haematocrit rise > 20% over baseline
DHF IV (DSS)	Profound shock with undetectable blood pressure/ pulse	Platelet count < 1,00,000 /cu.mm + Haematocrit rise > 20% over baseline

c. Investigations and Diagnosis

2. Grading of severity, case classification

3. Management and Disease Notification

4. Prevention of Dengue

1. Assessment:[42]

a. Obtain complete history:

- Onset of fever/ illness,
- Associated symptoms: diarrhea, respiratory
- Fluid intake and Urine output
- Warning signs
- Prior episodes of dengue
- Travel history, Family history
- Presence of co-existing conditions: infancy, pregnancy, obesity, diabetes mellitus, hypertension

b. Evaluation:

- Hemodynamic status: heart rate, capillary refill, skin color and temperature, peripheral pulse volume, pulse pressure, blood pressure, mentation.
- Hydration status
- Bleeding manifestations, Rash, positive tourniquet test
- Evidence of plasma leakage: pleural effusions, ascites, hemoconcentration, abdominal tenderness, hepatomegaly, acidotic breathing

c. Investigations: All patients:

i. Complete Blood count including Hematocrit

ii. Dengue serology for diagnosis:[43]

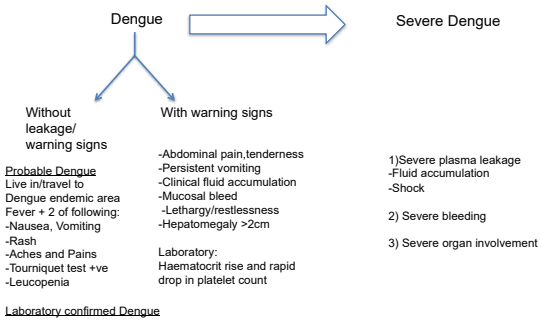
- NS1 Ag is a marker of acute dengue infection :first 3 days of illness.
- Single sample after day 5 : Specific IgM detection, upto 3 months after onset of fever.
- Primary infection : High IgM,Low IgG.
- Secondary infection : Low IgM, High IgG

iii. Specific tests:

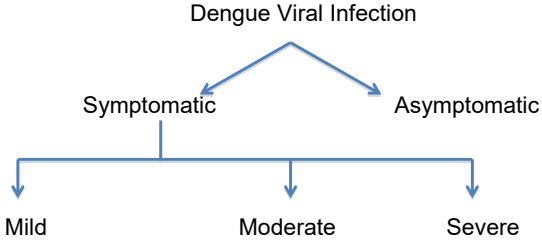
- Blood Sugar Level
- Organ Function tests
- Coagulation profile
- Blood culture

2. Grades:[44]

2009 WHO case classification for Dengue[45]

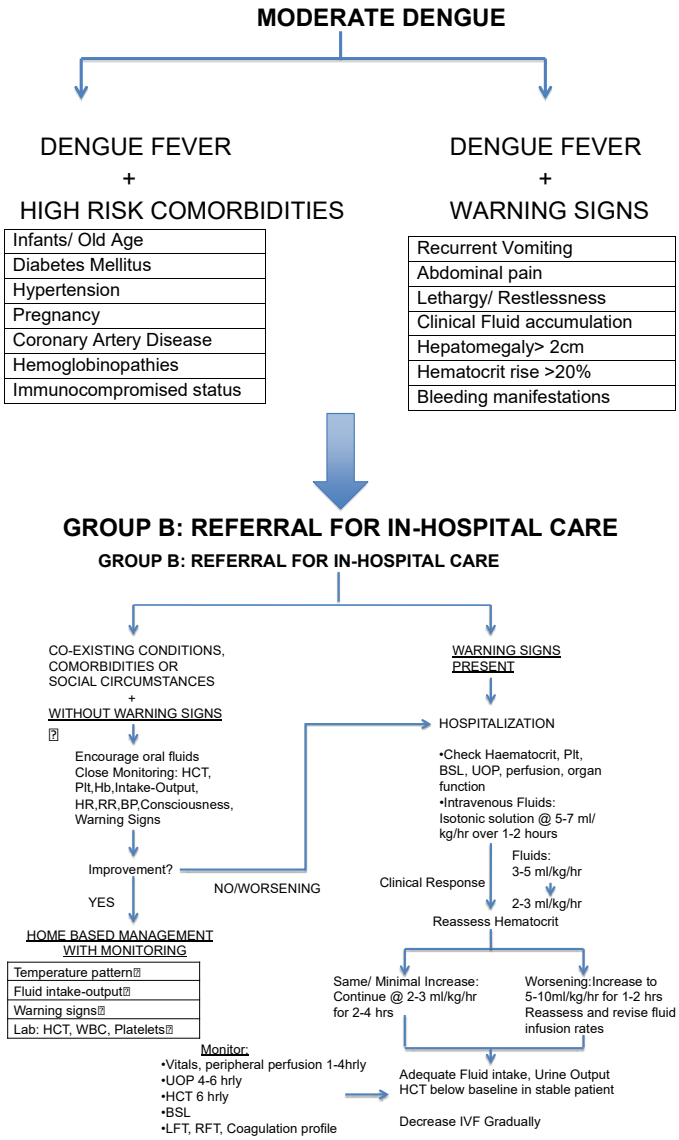


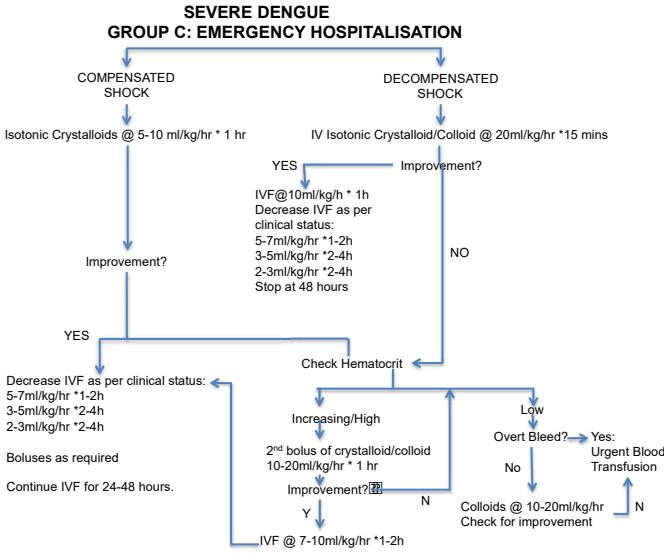
Management algorithms:
(Adapted from 46)



Mild Dengue / Dengue Without Warning Signs
Undifferentiated
Fever without complications/warning signs
Fever without evidence of capillary leakage
No comorbid conditions

Group A: Home Management		
Criteria	**Management**	
No warning signs	Bed rest	Daily Review for disease progression
Adequate oral fluid intake	Adequate fluid intake	Warning signs
Good urine output (every 6 hours)	Paracetamol upto 4gm/day	Home care card





Criteria for discharge[45]

1. Afebrile > 48 hours
2. Clinical improvement
3. Platelet count increasing
4. No Respiratory distress
5. Stable haematocrit without intravenous fluids

The principal underlying the treatment of dengue is the correction of the volume contraction in the vascular system due to the capillary leak syndrome. This has been shown to correspond to the risk of complications. Early and continual assessments of the fluid volume status as reflected in changes to haematocrit is reasonably accurate to follow.

It is important to ensure that patients do not have a sudden rise in values during the critical phase of capillary leak. The approach to dehydration depends on clinical scenario and the severity of volume loss during evaluation. This determines the speed of replacement of volume and additional measures for support.

Most patients can be managed at home with daily outpatient reviews with a checklist to assess severity and alarm symptoms. This can prevent overcrowding of hospitals without endangering patient care. However, it is important to remember that the risk of complications is most just after the patient becomes afebrile, and appropriate counseling is imperative to ensure that monitoring is continued into this critical phase.

Patients who may be at risk, including those with other medical conditions may be best cared for in the wards of hospitals, where regular monitoring and hydration should suffice. Patients with severe symptoms are best managed in areas with access to good monitoring and intervention services.

For most patients, only crystalloids are required for volume expansion, and colloids including blood may be considered in those in the most severe category. The role of platelets is minimal, if any, and is best restricted to those with active bleeding.

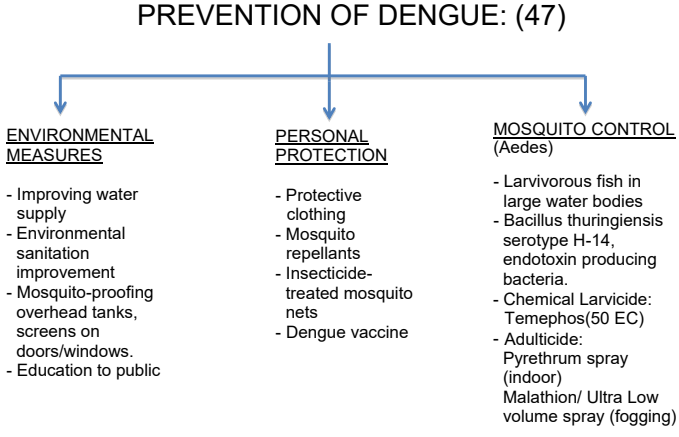
Discharge may be considered once the patient has crossed the critical phase. Again, those with difficulty handling the volume that is reabsorbed, like those with renal or

High risk	Low risk
Recent CAG with stenting <3mn	Stable CAD or stenting > 6mn previously
Mechanical valve	Biological valve
Chronic AF with past history of thromboembolism	Chronic AF without risk factors
Multiple risk factors for thromboembolism	
• Already on antiplatelets: • Should be continued • In case of significant bleed, Platelet count <50,000 or patient in shock: stop medications • Patient on Warfarin: withhold and do serial coagulation parameters. When INR below therapeutic range, heparin bridging and monitor	• Withhold aspirin and consider withholding clopidogrel and warfarin for one week, with close monitoring.

cardiac disease, may need additional observation during this phase as well.

Patients may experience additional manifestations during the recovery phase in addition to post viral asthenia like pruritus, joint pain and bradycardia. These tend to resolve spontaneously over time, and may only require reassurance.

There are many unusual manifestations of dengue, and should be considered in all patients with a short febrile illness. Raised liver enzymes are very common, and usually the AST is higher than ALT. However, severe liver injury is rare. Other unusual manifestations include Gullian-Barre syndrome, myocarditis, renal failure, and lung injury. In most cases, these resolve with appropriate symptomatic management.



Special circumstances

1. Dengue in immunocompromised patients:

- Patients on cancer chemotherapy
- Patients with haematological disorders
- Post transplant patients on immunosuppression
- Primary/congenital immunodeficiency disorders
- Chronic steroid therapy
- Autoimmune diseases on immunomodulator therapy
- HIV/AIDS with CD4 count <500

Clinical presentation is similar in immunocompromised patients, although the course is usually prolonged.[48] Principles of treatment remain the same, although close monitoring is preferred.

Transplant and Dengue: In post-solid organ transplant patients, dengue usually follows a benign course with no evidence of longterm damage / rejection episodes.[49,50] Thrombocytopenia is more severe in patients receiving steroids, azathioprine and cyclosporine concomitantly. Tacrolimus is found to prolong duration of thrombocytopenia.[50] Graft survival and outcome following dengue fever was not affected in the studies.

In studies involving renal transplant recipients, likelihood of developing severe forms of dengue was found to be low, probably due to diminished T-cell responses.[51]

There are reports of dengue in stem cell recipients, sometimes donor-derived.[52,53] Dengue fever complicating patients with aplastic anemia have been salvaged with stem cell therapy.[54] However, this disease appears to be more severe in this population and poor outcome is reported.

A case series of patients on biotherapy for rheumatological diseases, infected with dengue, found that none of them developed severe dengue.[55] However there are no guidelines regarding continuing biological therapy during the course of treatment.

2. Dengue in Pregnancy:

- High index of suspicion for diagnosis is necessary as the consequences due to dengue infection are multifold.[56] Multiple studies have shown complications ranging from miscarriages, preterm births, haemorrhages in labour, perinatal deaths, adverse maternal outcomes and vertical transmission of infection to the fetus.[57,58]
- Serial Haematocrit measurement is crucial for disease monitoring.[59]
- Unless imperative, to avoid induction of labour / Caesarian section during critical phase, as risk of bleeding is at its peak during that period.
- Baby should be evaluated and monitored post-

delivery as vertical transmission of disease has been observed.[9,60]

- Breastfeeding has been shown to transmit dengue in a case study, however there are no clear guidelines on the same.[61]

3. Dengue in patients on Antithrombotic treatment:[62]

4. Surgery and Dengue:

   Acalculous cholecystitis due to plasma leakage leading to gall bladder wall edema is a clinical manifestation of Dengue Fever. The patient presents with right hypochondrial pain. The course is usually self-limiting and surgery is not warranted unless there is diffuse peritonitis.[63]

   There are no guidelines on management of surgical patients with Dengue. Post-operative bleeding from surgical sites should be closely monitored. As removal of in-dwelling vascular catheters may cause hemorrhage, it could be deferred till critical phase is over. Platelet transfusion is not necessary in all surgical patients.[64]

5. Dengue and Diabetes Mellitus: Diabetes Mellitus is an independent risk factor for developing profound thrombocytopenia and severe forms of dengue infection.[65,66] Studies have shown DM to be a predictor of mortality in dengue.[66,67] A study has shown that stress-induced hyperglycemia found at the time of acute infection disappeared after recovery, warranting use of HbA1c for checking glycemic status. (68) Early diagnosis of dengue in diabetics is hence of importance. It will ensure closer glycemic control and adjusted fluid management in this population.

6. Dengue and Zika: Zika virus (ZIKV), an emerging arboviral infection also transmitted by Aedes spp belonging to genus Flavivirus is an important public health issue.[69]

   A recent report on coinfection between dengue and Zika raised the concern of missed / under-diagnosis of Zika. The effect of coinfection needs to be studied further.[70]

   Data suggests that there is an interplay between host antibody response to ZIKV and DENV, with concern of DENV being a cofactor for increasing severity of Zika infection.[71]

   There is speculation that this could affect how Zika behaves in pregnant women, and more research on this is ongoing.

   That dengue has become a major public health issue is beyond doubt; following well established protocols and pathways for assessment and management is the only way to reduce the morbidity, mortality and the financial impact of this disease, not to mention the overcrowding of already over burdened medical facilities.

REFERENCES

1. Gubler DJ. The global pandemic of dengue/dengue haemorrhagic fever: current status and prospects for the future. *Ann Acad Med Singapore* 1998; 27:227–234.
2. Stanaway JD, Shepard DS, Undurraga EA, Halasa YA, et al. The global burden of dengue: an analysis from the Global Burden of Disease Study 2013. *Lancet Infect Dis* 2016; 16:712-23.
3. Messina JP, Brady OJ, Scott TW, Zou C, Pigott DM, Duda KA, et al. Global spread of dengue virus types: mapping the 70 year history. *Trends Microbiol* 2014; 22:138-46.
4. Shepard DS, Undurraga EA, Halasa YA, 2013. Economic and disease burden of dengue in Southeast Asia. *PLoS Negl Trop Dis* 2013; 7:e2055.
5. National Vector Borne Disease Control Programme, 2013. Dengue Cases and Deaths in the Country since 2007. Ministry of Health and Family Welfare, Directorate General of Health Services. Available at: http://www.nvbdcp.gov.in/den-cd.html.
6. Thomas SJ, Endy T, Rothman A, Barrett A. Flaviviruses (Dengue, Yellow Fever, Japanese Encephalitis, WestNile Encephalitis, St Louis Encephalitis, Tick-Borne Encephalitis, Kyanasur Forest Disease, Alkhurma Hemorrhagic Fever, Zika) In: Bennett JE, Dolin R, Blaser M, editors. Mandell, Douglas, and Bennett's principles and practice of infectious diseases. 8th ed. Philadelphia: Elsevier Churchill Livingstone; c2015. p. 1881-1903.
7. Stramer SL, Linnen JM, Carrick JM, Foster GA, Krysztof DE, Zou S, et al. Dengue viremia in blood donors identified by RNA and detection of dengue transfusion transmission during the 2007 dengue outbreak in Puerto Rico. *Transfusion* 2012; 5298:1657-66.
8. Gupta RK, Gupta G, Chorasiya VK, Bag P, Shandil R, Bhatia V, et al. Dengue Virus Transmission from Living Donor to Recipient in Liver Transplantation: A Case Report. *J Clin Exp Hepatol* 2016; 6:59-61.
9. Chye JK, Lim CT, Ng KB, Lim JM, George R, Lam SK. Vertical transmission of dengue. *Clin Infect Dis* 1997; 25:1374-7.
10. Kalayanarooj S, Vaughn DW, Nimmannitya S, Green S, Suntayakorn S, Kunentrasai N, et al., Early clinical and laboratory indicators of acute dengue illness. *J Infect Dis* 1997; 176:313–321.
11. Srikiatkhachorn A, Krautrachue A, Ratanaprakarn W, Wongtapradit L, Nithipanya N, Kalayanarooj S, et al., Natural history of plasma leakage in dengue hemorrhagic fever: a serial ultrasonic study. *Pediatr Infect Dis J* 2007; 26:283–290.
12. Sen MK, Ojha UC, Chakrabarti S, Suri JC. Dengue Hemorrhagic fever (DHF) presenting with ARDS. *Indian J Chest Dis Allied Sci* 1999; 41:115-119.
13. Setlik RF, Ouellette D, Morgan J, McAllister KC, Dorsey D, Agan BK, et al. Pulmonary hemorrhage syndrome associated with an autochthonous case of dengue hemorrhagic fever. *South Med J* 2004; 97:688-92.
14. Promphan W, Sopontammarak S, Pruekprasert P et al. Dengue myocarditis. *Southeast Asian J Trop Med Public Health* 2004; 35:611-3.
15. Veloso HH, Ferriera JA, Paiva JM, Honorio JF, Bellei NC, Paola AA. Acute atrial fibrillation during dengue hemorrhagic fever. *Braz J Infect Dis* 2003; 7:418–422.
16. Lum LC, Lam SK, Choy YS, George R, Harun F. Dengue

encephalitis: a true entity? *Am J Trop Med Hyg* 1996; 54:256–9.

17. Solomon T, Dung NM, Vaughn DW, Kneen R, Raengsakulrach B, Loan HT, et al. Neurological manifestations of dengue infection. *The Lancet* 2000; 355:1053-9.
18. Soares CN, Faria LC, Peralta JM, De Freitas MR, Puccioni-Sohler M. Dengue infection: neurological manifestations and cerebrospinal fluid (CSF) analysis. *J Neurol Sci* 2006; 249:19–24.
19. Martinez-Torres E, Polanco-Anaya AC, Pleites-Sandoval EB. Why and how children with dengue die? *Rev Cubana Med Trop* 2008; 60:40–47.
20. Wu KL, Changchien CS, Kuo CM, Chuah SK, Lu SN, Eng HL et al. Dengue fever with acute acalculous cholecystitis. *Am J Trop Med Hyg* 2003; 68:657–660.
21. Ooi ET, Ganesananthan S, Anil R, Kwok FY, Sinniah M. Gastrointestinal manifestations of dengue infection in adults. *Med J Malaysia* 2008; 63:401–405.
22. Lum LC, Lam SK, George R, Devi S., Fulminant hepatitis in dengue infection. *Southeast Asian J Trop Med Public Health* 1993; 24:467-71.
23. Chen TC, Chen TC, Perng DS, Tsai JJ, Lu PL, Chen TP. Dengue Hemorrhagic Fever complicated with pancreatitis and seizure. *J Formos Med Assoc* 2004; 103:865–868.
24. Tsai CJ, Kuo CH, Chen PC, Changcheng CS. Upper gastrointestinal bleeding in dengue fever. *Am J Gastroenterol* 1991; 86:33–35.
25. Miranda LE, Miranda SJ & Rolland M. Case Report: Spontaneous Rupture of the Spleen Due to Dengue Fever. *Braz J Infect Dis* 2003; 7:423–425.
26. Wiwanitkit V. Acute Renal Failure in the Fatal Cases of Dengue Hemorrhagic Fever, a Summary in Thai Death Cases. *Renal Failure* 2004; 27:647-.
27. Wiersinga WJ, Scheepstra CG, Kasanardjo JS et al. Dengue fever induced hemolytic uremic syndrome. *Clin Infect Dis* 2006; 43:800–801.
28. Potts JA, Rothman AL. Clinical and laboratory features that distinguish dengue from other febrile illnesses in endemic populations. *Trop Med Int Health* 2008; 13:1328-40.
29. Daumas RP, Passos SR, Oliveira RV, Nogueira RM, Georg I, Marzochi KB, Brasil P. Clinical and laboratory features that discriminate dengue from other febrile illnesses: a diagnostic accuracy study in Rio de Janeiro, Brazil. *BMC Infect Dis* 2013; 13:1
30. Kuo CH, Tai DI, Chang-Chien CS, Lan CK, Chiou SS, Liaw YF. Liver biochemical tests and dengue fever. *Am J Trop Med Hyg* 1992; 47:265-70.
31. Jaenisch T, Tam DT, Kieu NT, Ngoc T, Nam NT, Van Kinh N, et al. Clinical evaluation of dengue and identification of risk factors for severe disease: protocol for a multicentre study in 8 countries. *BMC Infect Dis* 2016; 16:1.
32. Epelboin L, Boullé C, Ouar-Epelboin S, Hanf M, Dussart P, Djossou F, et al. Discriminating malaria from dengue fever in endemic areas: clinical and biological criteria, prognostic score and utility of the C-reactive protein: a retrospective matched-pair study in French Guiana. *PLoS Negl Trop Dis* 2013; 7:e2420.
33. Parry CM, Wijedoru L, Arjyal A, Baker S. The utility of diagnostic tests for enteric fever in endemic locations. *Expert Rev Anti Infect Ther* 2011; 9:711-25.
34. Fisher RG, Boyce TG. Nonstreptococcal pharyngitis. In: Moffet´s Pediatric Infectious Diseases. A problem- oriented approach, 4th ed. Philadelphia, PA, Lippincott Williams and Wilkins, 2005: 34–35.
35. Flannery B, Pereira MM, De Codes LG, Dourado CM, Riley LW, Reis MG, et al., Referral pattern of leptospirosis cases during a large urban epidemic of dengue. *Am J Trop Med Hyg* 2001; 65:657–663.
36. Van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. *N Engl J Med* 2004; 351:1849-59.
37. Kularatne SA, Gihan MC, Weerasinghe SC, Gunasena S. et al., Concurrent outbreaks of Chikungunya and Dengue fever in Kandy, Sri Lanka, 2006-07: a comparative analysis of clinical and laboratory features. *Postgrad Med J* 2009; 85:342–346.
38. Watt G, Jongsakul K, Chouriyagune C, Paris R. Differentiating dengue virus infection from scrub typhus in Thai adults with fever. *Am J Trop Med Hyg* 2003; 68:536-8.
39. Keighley CL, Saunderson RB, Kok J, Dwyer DE. Viral exanthems. Curr Opin Infect Dis. 2015 Apr 1;28(2):139-50.
40. Premaratna R, Bailey MS, Ratnasena BG, De Silva HJ. Dengue fever mimicking acute appendicitis. *Trans R Soc Trop Med Hyg* 2007; 101:683-5.
41. Cabié A, Abel S, Lafaye JM, Béra O, Césaire R, Sobesky G. Dengue or acute retroviral syndrome?. *Presse Med* 2000; 29:1173-4.
42. Martinez TE. Preventing deaths from dengue: a space and challenge for primary health care. *Rev Panam Salud Publica* 2006; 20:60–74.
43. Buchy F, Yoksan S, Peeling RW, Hunsperger E. Laboratory tests for the diagnosis of dengue virus infection.TDR/ Scientific Working Group.TDR/SWG/08 Geneva, Switzerland. 2006 Oct (1): 74–85.
44. Deen JL, Harris E, Wills B, Balmaseda A, Hammond SN, Rocha C, et al. The WHO dengue classification and case definitions: time for a reassessment. *Lancet* 2006; 368:170–3.
45. World Health Organization, Special Programme for Research, Training in Tropical Diseases, World Health Organization. Department of Control of Neglected Tropical Diseases, World Health Organization. Epidemic, Pandemic Alert. Dengue: guidelines for diagnosis, treatment, prevention and control. World Health Organization; 2009.
46. WHO, 2013. Handbook on Dengue Clinical Management. Available at: http://apps.who.int/iris/bitstream/10665/76887/1/9789241504713_eng.pdf
47. Gupta N, Srivastava S, Jain A, Chaturvedi UC. Dengue in India. *Indian J Med Res* 2012; 136:373.
48. Sharma SK, Seth T, Mishra P, Gupta N, Agrawal N, Broor S, et al. Clinical profile of dengue infection in patients with hematological diseases. *Mediterr J Hematol Infect Dis* 2011; 3.
49. Azevedo LS, Carvalho DB, Matuck T, Alvarenga MF, Morgado L, Magalhaes I, et al. Dengue in renal transplant patients: a retrospective analysis. *Transplantation* 2007; 84:792-4.
50. Weerakkody RM, Palangasinghe DR, Dalpatadu KP, Rankothkumbura JP, Cassim MR, Karunanayake P. Dengue fever in a liver-transplanted patient: a case report. *J Med Case Rep* 2014; 8:1.
51. Franco-Paredes C, Jacob JT, Hidron A, Rodriguez-Morales

AJ, Kuhar D, Caliendo AM. Transplantation and tropical infectious diseases. *Int J Infect Dis* 2010; 14:e189-96.

52. Visuthranukul J, Bunworasate U, Lawasut P, Suankratay C. Dengue hemorrhagic fever in a peripheral blood stem cell transplant recipient: the first case report. *Infect Dis Rep* 2009; 1:3.
53. Punzel M, Korukluoğlu G, Caglayik DY, Menemenlioglu D, Bozdag SC, Tekgündüz E et al. Dengue virus transmission by blood stem cell donor after travel to Sri Lanka; Germany, 2013. *Emerg Infect Dis* 2014; 20:1366.
54. Khoj L, Baksh R, Aslam M, Kelta M, Albeirouti B, Rehman JU. A Case of Dengue Fever-Induced Severe Aplastic Anemia Salvaged by Allogeneic Bone Marrow Transplant. *J Leuk* 2013; 2013.
55. Deligny C, de Bandt M, Dehlinger V, Numéric P, Cabié A, Lombard F et al. Dengue fever in patients under biologics. *J Clin Virol* 2014; 61:442-3.
56. Pouliot SH, Xiong X, Harville E, Paz-Soldan V, Tomashek KM, Breart G, Buekens P. Maternal dengue and pregnancy outcomes: a systematic review. *Obstet Gynecol Surv* 2010; 65:107-18.
57. Restrepo BN, Isaza DM, Salazar CL, Ramirez JL, Upegui GE, Ospina M et al. [Prenatal and postnatal effects of dengue infection during pregnancy]. *Biomedica* 2003; 23:416-23.
58. Waduge R, Malavige GN, Pradeepan M, Wijeyaratne CN, Fernando S, Seneviratne SL. Dengue infections during pregnancy: a case series from Sri Lanka and review of the literature. *J Clin Virol* 2006; 37:27-33.
59. Bunyavejchevin S, Tanawattanacharoen S, Taechakraichana N, Thisyakorn U, Tannirandorn Y, Limpaphayom K. Dengue hemorrhagic fever during pregnancy: antepartum, intrapartum and postpartum management. *J Obstet Gynaecol Res* 1997; 23:445-8.
60. Thaithumyanon P, Deerojnawong J, Innis BL. Dengue infection complicated by severe hemorrhage and vertical transmission in a parturient woman. *Clin Infect Dis* 1994; 18:248-9.
61. Barthel A, Gourinat AC, Cazorla C, Joubert C, Dupont-Rouzeyrol M, Descloux E. Breast milk as a possible route of vertical transmission of dengue virus? *Clin Infect Dis* 2013; 57:415-7.
62. Verdeal JC, Costa Filho R, Vanzillotta C, Macedo GL, Bozza FA, Toscano L, et al. Guidelines for the management of patients with severe forms of dengue. *Rev Bras Ter Intensiva* 2011; 23:125-33.
63. Beniwal P, Kumar S, Gulati S. Acalculous cholecystitis in dengue fever. *Indian Journal for the Practising Doctor* 2000; 3:2006-08.
64. Arya SC, Agarwal N. Dengue fever in a patient recovering from coronary artery bypass grafting. *Ann Card Anaesth* 2011; 14:245
65. Chen CY, Lee MY, Lin KD, Hsu WH, Lee YJ, Hsiao PJ, Shin SJ. Diabetes Mellitus Increases Severity of Thrombocytopenia in Dengue-Infected Patients. *Int J Mol Sci* 2015; 16:3820-30.
66. Pang J, Salim A, Lee VJ, Hibberd ML, Chia KS, Leo YS, et al. Diabetes with hypertension as risk factors for adult dengue hemorrhagic fever in a predominantly dengue serotype 2 epidemic: a case control study. *PLoS Negl Trop Dis* 2012; 6:e1641.
67. Karunakaran A, Ilyas WM, Sheen SF, Jose NK, Nujum ZT. Risk factors of mortality among dengue patients admitted to a tertiary care setting in Kerala, India. *J Infect Public Health* 2014; 7:114–20.
68. Hasanat MA, Ananna MA, Ahmed MU, Alam MN. Testing blood glucose may be useful in the management of dengue. *Mymensingh Med J* 2010; 19:382–5.
69. Joob B, Wiwanitkit V. Zika virus infection and dengue: A new problem in diagnosis in a dengue-endemic area. *Annals of Tropical Medicine and Public Health* 2015; 8:145-6.
70. Dupont-Rouzeyrol M, O'Connor O, Calvez E, Daurès M, John M, Grangeon JP, et al. Co-infection with Zika and dengue viruses in 2 patients, New Caledonia, 2014. *Emerg Infect Dis* 2015; 21:381-2.
71. Dejnirattisai W, Supasa P, Wongwiwat W, Rouvinski A, Barba-Spaeth G, Duangchinda T, et al. Dengue virus sero-cross-reactivity drives antibody-dependent enhancement of infection with zika virus. *Nat Immunol* 2016.