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Management of Dengue Viral Infection in Endemic Resource Limited Countries

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Abstract

Dengue fever is a common epidemic / endemic disease worldwide especially in under-developed countries and tropical areas. It has serious health, economical and epidemiological issues. If it's not managed properly, the mortality rate can be high. It's often confused with other acute infectious diseases such as chikungunya, malaria, typhoid and COVID. This diagnostic confusion is a big issue especially in resource limited countries where these are common, and sometimes these diseases can co-exist as well. These infectious diseases make a very difficult clinical puzzle that can mimic many other diseases as well and pose a great difficulty for the patient's management. As a result, many patients may be over treated for all these possibilities leading to antibiotic resistance, increased cost of treatment and prolonged illness. With proper management the mortality can be reduced.

It's important to understand these diseases for managing patients with these infections, which almost every doctor see in clinical practice. This review article aims to provide insight into the pathogenesis of Dengue, its various manifestations, clinical approach for its differential diagnosis and its management considering recent evidence.

Keywords: Dengue fever, dengue haemorrhagic fever, fever with rigours, acute infectious emergencies.

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Introduction

Dengue fever is one of the most common & serious public health epidemic / endemic infectious issues for the past few decades.[1] It's a viral infection caused by bite of female aedes mosquito. Approximately 400 million cases and 22000 deaths occur due to dengue every year, more common in tropical & subtropical regions.[2] In our countries of Indo-Pak subcontinent, Dengue is very prevalent due to overcrowding, poverty, lack of sanitation, and the abundance of suitable breeding places to promote prevalence of the mosquitoes.[3]

Dengue Virus (DENV)

Dengue virus belongs to Flavivirus group. It is a spherical 50 nm virus made up of three structural proteins (nucleocapsid, pre membrane / membrane & envelope proteins), a lipid bilayer envelope and positive stranded RNA. The virus also has seven non-structural (NS) proteins (NS1, NS2A, NS2B, NS3, NS4A, NS4B, & NS5).[4] Dengue viruses have five serotypes, DENV[1-5] with different antigens & genotypes. Each serotype has many subtypes due to mutations. Infection with any serotypes produces immunity against the serotype only. However subsequent infection by other serotypes is more severe due to antibody-dependent enhancement of immune response, elaborated in the pathophysiology section.[4]

Transmission & Incubation Period

It's transmitted by Aedes mosquito bite and isn't a contagious disease. It's also not transmitted by droplets or aerosols. The mosquito is more active during daytime. Incubation period is usually 3-10 days after the bite by infected misquotes. The disease infects animals and humans both.[5] Animal disease is transmitted by a different subtype of Aedes mosquito.

Risk factors includes previous infection with dengue which increases risk of severe dengue. Urbanisation, especially unplanned, promotes dengue transmission through multiple factors: population density, human mobility, access to reliable water sources, water storage & sewerage. Public awareness, knowledge, and attitude toward the mosquito & dengue also contributes. Climate change may also shift the risk in tropical & subtropical

areas.[5]

Pathophysiology of the Infection

The virus replicates in dendritic cell present in the skin, and infects macrophages, monocytes & lymphocytes. Virus enters these cells by cell surface proteins such as Fc receptors, lipopolysaccharide binding molecules, glycosaminoglycans, & heparin sulphate etc. The virus replicates inside these cells by using host energy system, enzymes and cellular machinery needed for duplicating RNA & viral proteins. Then the virus will exit the cell to infect new cells.[6]

Immune system & the virus:

Innate immune system tries to fight with the virus by producing interferon alpha & beta, interleukins, and various other cytokines. Humoral and cellular immune system specifically targeting the virus develops in 5-7 days. All this virus-specific response is co-ordinated by T-helper cells (CD-4) which identify the virus infected antigen presenting cells (APC) such as macrophages. Antigen presenting cells have MHC-II on their surface to interact with CD-4 cells. These MHC-II on APCs holds and presents viral antigens to the T-helper cells. Activated CD-4 cells then activate B-cells & cyto-toxic T-cells (CD-8) to initiate virus specific immune response. IgM is produced by B-cells as an acute response, followed by IgG for long term immunity. Cyto-toxic T-cells (CD-8) cells fight with the virus infected cells by producing various cytokines and by direct attack on the infected cells. The CD-8 cells identify the infected cells with help of MHC-I on the cell surface which interacts with CD-8. MHC-I on infected cells holds & presents viral antigens to cyto-toxic T-cells. Memory T-cells are produced as well for future immunity and response.[7,8]

How the virus escapes immunity?

The virus escapes immunity by targeting immune mediators & prevents intracellular antiviral signal transduction. The virus resides insides the vesicles. Viral NS-5 protein caps it's RNA which mimics like host cell mRNA and escapes degradation. NS proteins also inhibits various intra cellular signals to hide virus detection by immune surveillance. NS-1 helps in viral replication & inhibits complement activation. NS-1 antigen also activates macrophages which damage endothelium. NS-1 antigen and antibody against NS-1 leads to production of many cytokines leading to dengue haemorrhagic fever (DHF). NS-1 antigen binds with platelets and induce apoptosis. NS2 & 4 are also involved in the viral replication.[6,7,8,9]

Why the subsequent infections are more severe?

Memory T-cells from the previous infection will produce more cytokines such as IL-1, IL-2, IL-10, TNF-alpha & interferon gamma adding to the severity of the subsequence infections. Also, the cross-reacting antibodies present at the time of subsequent infections bind with the virus without neutralising it and promotes its entry into the macrophages by using Fc receptors on these monocytes. There are four serotypes of the virus and it's likely that a patient can get re-infected with a different serotype of the virus despite having dengue previously. However, re-infection with the same serotype is unlikely. Usually, subsequent episodes of the disease are more severe.[7,8,9,10,11]

How the virus cause disease?

It's infection of the blood (viremia) & blood cells which can causing vascular endothelial damage & subsequently organ seeding as well. It doesn't come through lungs or GIT, hence prodromal symptoms related to respiratory tract or GIT, a very common scenario with majority of other viruses is not the case with dengue. The damage to vascular endothelium will cause leakiness or even rupture of the capillaries. Endothelium damage will also predispose to coagulopathy, tissue ischemia, & contributes to cytopenia etc. Leaky capillaries, rupture of capillaries &/or blockage of capillaries are the reason behind all the manifestations of severe dengue fever.[9,10,11,12]

Clinical Manifestations of Dengue Virus Infection

There are three clinical patterns of dengue infection:

1): Dengue fevers: it's an acute infection period from day 2-7, with three phases: febrile, critical & convalescent phase. Febrile phase has high grade fever & dehydration, and usually lasts for 2-7 days. It's viremic infection & unlike COVID and most other viruses which often start with respiratory symptoms, dengue enters blood directly by mosquito bite. Hence respiratory or GIT-related viral prodromal is often missing in dengue. Because it's viremia so the temperature often goes very high 39-40 or even above. As the infection is in the blood which doesn't find exit to escape it causes rigours too. Rigours are not common with many viruses, but viruses often cause chills. Viruses which cause rigours are dengue, chikungunya, & COVID. Other viruses are rare to cause rigours unless they have severe viremia. Dengue is also called as bone-breaking fever as the pain is a major symptom and quite severe almost mimicking severity of fracture-related pain. Headache, orbital pain, bone pains, joint pains, muscle aches are common. Bone pains are due to bone ischemia and even infarcts. Abdominal pain may indicate liver involvement and should caution for leaky syndrome. Intestinal ischemia will cause pain, bleeding etc. Skin rash is common and is mainly due to inflammation of the skin capillaries. Convalescent phase is recovery period & may have rash, itching and increased appetite.[9,11,12] Fig.1.

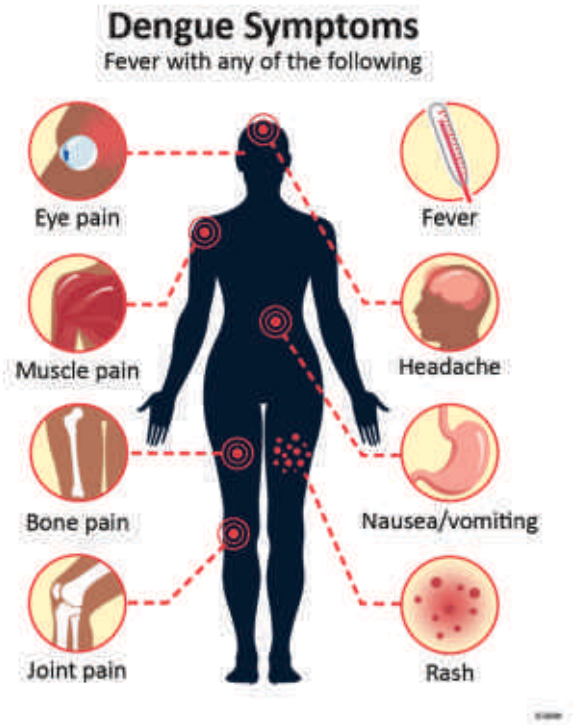

Fig. 1; *Dengue symptoms; Photo taken from CDC-Website.*

Dengue haemorrhagic fever & Dengue shock syndrome

Capillary leakage and even damage caused by the endothelial infection is the underlying reason for many of the complications. Capillary occlusion due to swollen endothelium also causes tissue ischemia and severe pain (bone infarcts, muscle infarcts etc). Plasma leakage into the tissues leads to haemoconcentration (rising haematocrit), hypovolemia (low BP, tachycardia etc), and fluid accumulation in tissues (oedema, ascites, pleural effusions etc). Rupture of capillary causes bleeding. Low platelet counts and infection related coagulopathy can also add on to the bleeding. Endothelial damage also causes hyper coagulable state and coagulopathy. Viremia related bone marrow suppression, & organ damage can also cause issues like hepatitis, pneumonitis, meningoencephalitis etc.[6,8,12]

Alarming Clinical Symptoms & Signs

- Hypovolemia (low BP, increased capillary refill time, tachycardia, weak thready pulse, narrow pulse pressure etc).
- Haemoconcentration (rising haematocrit) & tissue fluid accumulation (ascites, hepatic congestion, pleural effusion, subcutaneous oedema etc).
- Cytopenia (low platelet counts, leucopenia, anaemia)
- **Hepatitis:** Liver involvement can cause abdominal pain, nausea, vomiting, jaundice and deranged LFTs.
- Lung involvement presents with tachypnoea, desaturation, chest pain, cough etc due to fluid leakage, viral pneumonia, pleural effusion, pulmonary oedema o &/or ARDS.
- Meningoencephalitis: Brain involvement such as encephalitis is less common but serious complications.
- Coagulopathy
- Bleeding (drop in Hb & haematocrit).

So, monitoring for the above alarming symptoms or signs is very important: if none of the above is there, the patient is stable. If any or many of the above, it should alert to monitor for the complications. Above complications are also given different names such as Dengue Pre-Shock, Dengue Leaky Syndrome, Dengue Haemorrhagic Fever, Dengue Shock etc. But all these means that the patient needs monitoring n management as inpatient likely in intensive care depending on the clinical situation. The most useful test for monitoring n managing Dengue fever patient is haematocrit (Hct):

Dengue Haemorrhagic Fever (DHF) is ongoing fever for 2-7 days associated with haemorrhage with platelet counts <100000 cells/cu mm & hemoconcentration (rise in HCT >20% from the normal baseline of a healthy individual of the same age). It's due to increased vascular permeability, leakage &/or rupture. Cytokine storm is the main culprit behind DHF & DSS. Dengue Shock Syndrome (DSS) is severe form of dengue haemorrhagic fever. It's hypovolemia shock which can lead to multi organ failure.[9,11,12,13] Fig .2

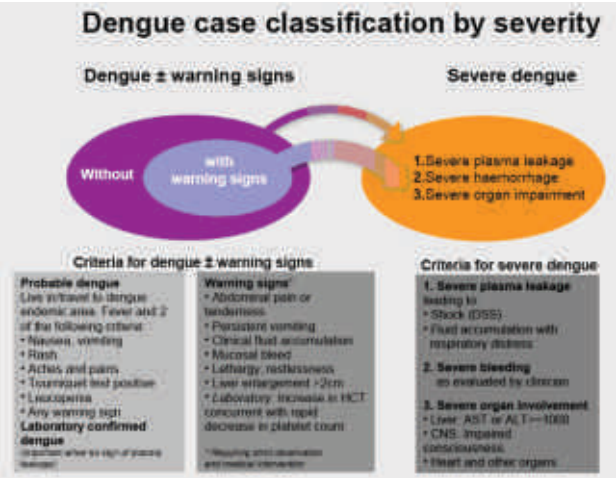

Fig. 2: *The revised WHO dengue case classification photo credit NSW Health, Australia.*

Differential Diagnosis of Dengue Fever in Endemic Areas

1): Chikungunya infections & malaria resembles closely

with dengue as all are infections of the blood and are transmitted by mosquito bite. Also, they cause high grade fever with rigours and no localising symptoms at the start of the disease. However, acute malaria usually gives one spike of fever repeating every 24-48 hours depending on the subtypes of the plasmodium. Also, early splenomegaly on day 2-3 is more with malaria as it infects RBCs. Malarial parasite can be detected on blood film. Chronic malaria slows down, rigour disappear due to low grade infection, splenomegaly becomes massive, and fever doesn't happen at regular intervals anymore as now multiple life cycles of the parasite are running and patient will have multiple spikes of temperature without rigours. Dengue will cause multiple spikes of high-grade fever with rigours, and pain is often a dominant symptom. As it's not infection of the RBC, early splenomegaly isn't there. As it damages capillary endothelium, hence fluid leakage out of capillaries, hypovolemia and shock are likely with severe dengue. Bleeding can also occur due to capillary rupture. Capillary occlusion will cause ischemia of the bones, joints n muscles, leading to severe muscle and bone pains. The pain can be as severe as that of a fracture; hence it's also called as bone breaking fever.[13,14,15]

2): Bacterial infections especially contained infections where toxins don't find an exit other than being spilled into the blood leading to multiple spikes of high-grade fever associated with rigours. Examples are acute pyogenic abscess, bacteremic infections, endocarditis, cholangitis with obstruction, pyelonephritis, pneumonia, meningitis etc. Localising clues, positive blood cultures, high CRP help differentiate bacterial infection from the viral cause. Typhoid is slowly increasing bacterial entry into the blood from the ileum. It doesn't cause damage or infection of the ileum in first week. As it's slowly increasing bacteraemia, hence it does not usually cause rigours. Patient will have fever increasing every day, multiple spikes in 24 hours, not usually touching the baseline but without rigours. As ileum is not damaged & infection is in the blood, hence there are no localising symptoms related to GIT or any other organ in first few days. Organ seeding or organ specific complications only occur in late second or third week when infection gets complicated. By the end of second week of enteric infection, either the infection will start resolving or will complicate such as Ileal perforation, or organ seeding like pneumonia etc. But these complications don't happen in the first week of infection. Brucellosis can also have pattern like enteric, but at a bit slower pace and may last more than few weeks. Enteric would either complicate during second / third week or will be cured whereas brucellosis will continue for weeks.[16,17]

3): Cytopenia, capillary leakiness and /or bleeding can sometimes confuse with microangiopathies such as small vessel vasculitis, DIC, TTP, HUS, septic shock etc. This is especially true when patient present late in complicated stage. But associated clinical clues, course of the disease and lab should be helpful to differentiate. Also, the drop in cell counts, though common in dengue but can be seen in many viral infections, gram negative septicaemia, any infection complicated with coagulopathy like DIC &/or due to associated comorbidities of the patient including medications.[13,15,16]

4): Dengue vs COVID: Dengue starts from blood and then goes to other organs, hence non localising fever which effects on blood cell count, capillaries leakage (hypovolemia, hypotension, haemoconcentration & third spacing of the fluid in body cavities like pleural space), and /or capillary rupture with bleeding are main issues. Dengue is transmitted by mosquito bite (not through droplets). Hence mosquito exposure is there in dengue. Dengue causes high grade fever to start with & it is associated with shivering (rigours) & patient had multiple temperature spikes in 24 hours. Dengue doesn't affect taste or smell & doesn't usually cause sore throat that COVID does. COVID, transmitted by droplet & aerosols through respiratory system, hence classically starts as flue like illness (no rigours in early stage and fever gradually builds up in next 2-3 days. COVID involves upper & lower respiratory tract first and then spreads to blood and other organs. Hence lungs are the focus in COVID. COVID classically cause peripheral (sub pleural) opacities on HRCT or X-ray. Whereas dengue comes to lungs when it's complicated like ARDS Dengue doesn't cause peripheral (sub-pleural) lung involvement on X-ray or HRCT.

Dengue doesn't commonly make clots & hence clotting tests or D-Dimer are not high unless complicated by organ failure state. Dengue causes bleeding and capillary leakage (hence pleural effusions, ascites, skin oedema). COVID produces lot of cytokines affecting clotting system, makes clots and affects clotting tests & D-Dimer. CRP often goes high in COVID due to IL-6 produced by the infection, whereas dengue doesn't cause very high CRP. Blood counts (platelets & neutrophils) drops often in dengue. COVID can cause thrombocytopenia too. However, Haemoconcentration (high haematocrit) due to plasma leakage is seen in dengue but usually not in COVID. COVID also causes high ferritin, LDH, D-Dimers & IL-6. Dengue affects upper abdomen more like persistent vomiting, liver involvement, hepatomegaly, whereas COVID can present with viral gastroenteritis like picture in some cases. Dengue's cause severe bones and abdominal pain & the bone pain can be as worse as that of a fracture bone. COVID generally cause more muscle aches and pains or chest pain.[17,18,19,20]

Testing for viral antigens (NS1 etc for Dengue) & viral PCR can confirm too. For COVID, PCR may be negative

in patients where lungs are involved but upper airways are spared, hence PCR negatively doesn't exclude COVID in patients with classic lung involvement. Treatment is mainly supportive for both, but dexamethasone, anti-viral & immunosuppressants are recommended when COVID involves lungs or other organs whereas it's not recommended for dengue. Certainly, both can co-exist especially in Pakistan during this time. Tests and clinical judgement should be used.[21,22,23,24]

Diagnosis of Dengue

PCR testing is costly but gold standard. Virus is available in blood & blood cells during day 1-7 of the symptoms, more when the fever is there. Viral antigen (NS-1) is commonly available, rapid, and reliable test. Serology may indicate previous infection if IgG positive or acute infection if IgM positive. Rising titre of antibodies help confirm acute infection too. Serology however takes days to 1-2 weeks to be positive. NS-1 & IgM have cross reactivity with other Flaviviruses, hence are not fully reliable. NS-1 can be detected by ELISA. NS-1 & viral RNA can be detected from day 1-7, whereas IgM or IgG can be detected from day 4-5 onward.25 Fig.3.

Pancytopenia, anaemia, thrombocytopenia etc are common in many viral and non-viral illness and are not specific for dengue and does not mean dengue. Haematocrit is very important tool to monitor for leaky phase of dengue and for bleeding phase.

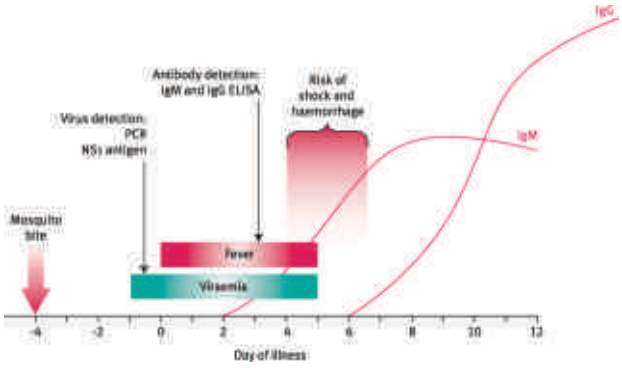

Fig. 3: *Typical primary dengue infection with timing of diagnostic tests Source: Tropical Regional Services, Queensland Health, Australia*

Treatment & Prevention for Dengue Infection

Must not do the followings

1. Transfuse platelets as they don't decrease the risk of bleeding.
2. Use steroids.
3. Use half normal saline.
4. Assume IV fluids are necessary.

Must do the followings

Table 1: *Comparison of main clinical differences of dengue from COVID, malaria & enteric fever.*

Clinical clues	Dengue	Malaria	Enteric	COVID-19
Mosquito bite	**Yes**	**Yes**	**No**	**No**
Respiratory prodrome	Unlikely	No	No	Yes
Predominant Lung involvement	No	No	No	Yes
High fever at start	Yes & multiple spikes /day	Yes, but 1 spike in 24- 48 hours	Slow rising, but multiple times a day	Slowly increases in intensity, multiple times / day
Rigours	Yes	Yes	Uncommon	May be when fever is high grade.
Pain	Very intense bone pain, joint, headache	Not a marked symptom	Not a marked symptom	Myalgias
Capillary leakiness	Yes	Uncommon, only if MOF	Uncommon, only if MOF	Uncommon, only if MOF
Abdominal issues	Acute hepatitis: tender oedematous liver & jaundice.	Early splenomegaly on day 2 or 3 of infection.	Transaminitis mainly, but acute hepatitis is uncommon	Acute gastroenteritis like picture may be there
Rash	May be	Uncommon	May be	May be
Blood Tests	Cytopenia, especially low platelets.	Coomb's negative Haemolytic anaemia	Normal or low WCC. High CRP	Cytopenia, High CRP
Diagnostic Tests	NS-1, PCR	MP slides	Blood culture	COVID PCR, HRCT chest

Abbreviations used: HRCT (high resolution CT) MOF (multi-organ failure), NS-1 (non-structural protein 1):

1. Educate the patient.
2. Monitor fluid intake, output, viral signs & Haematocrit.
3. Recognise worsening at early stage especially early shock.
4. Use colloids for refractory shock.
5. Transfuse RBCs or whole blood for bleeding.

Fluid management Table 2-7

CDC has given very useful guidelines for clinicians to manage dengue and its complications. The virus infects capillary endothelium and can cause leakiness of the vessels or even rupture. Leaking vessels will lead to less fluid inside the blood vessels but more fluid outside the vessels. This leads to intra vascular Hypovolemia causing haematocrit to rise and blood pressure to drop. Further leakage can cause hypotension and shock too. Hence giving hypotonic fluids (dextrose, 0.45% saline etc) can worsen. When fluids are needed, start with normal saline as sodium has osmotic force and can help to keep the fluid in the vessel. Choice of fluid and volume needed are decided based on haematocrit & clinical assessment of fluid status such as pulse, BP, capillary refill, urine output, underlying cardiac or respiratory condition etc. But if there is any blood test which will help guide us; the answer is Haematocrit.

Rising haematocrit would indicate ongoing leakiness of the plasma from the blood into the extra vascular space. Falling haematocrit would either indicate bleeding or too many fluids given. If haematocrit is going high, start with normal saline and keep checking haematocrit at regular intervals. If haematocrit is still going high, increase the normal saline. If it keeps going high despite normal saline and patient is worsening, start colloids such as Albumin. Change from the crystalloids to colloids or down stepping from colloids to crystalloids is based on haematocrit.[26,27] If haematocrit is dropping, patient needs pack RBC or whole blood transfusion.[26,27,28,29,30,31]

Bleeding & platelet counts

Platelets are not issue unless they are extremely low, and patient is bleeding. The platelet transfusion is very rarely needed, if at all. Replacing platelets is not needed in vast majority of dengue cases with low platelets. There is no need to create panic or hype and asking attendants to arrange platelets if the count is low, but patient isn't bleeding, or the count is still standing sufficient. Focus should mainly be on the fluid management, the real issue. Bleeding is mainly due to damage to capillaries and not due to thrombocytopenia. Hence platelet transfusion or the panic created by low platelet count is often unnecessary which diverts attention from the underlying issues of capillary leakiness / rupture.[26,28,29,30,31]

Additional supportive care

Patient may need additional supportive measures for organ involvement such as respiratory failure or liver failure. Patients' leaky syndrome, organ involvement or progressive disease should be managed in intensive care. There are no special antiviral drugs for dengue virus. Corticosteroids have no role in dengue cases unless the patient has adrenal haemorrhage related acute Addison's. NSAIDs and aspirin can complicate the situation by inhibition of the platelets, and by promoting GI bleeding. Fever should be treated with Panadol. Pain may need strong analgesic such as opioids.[26,27,28.29,30,31]

Preventive Measures for Dengue Infection

There is no effective vaccine available worldwide. Main reasons are rapidly occurring mutations of the virus. However, the risk of infection and its severity can be reduced by preventive measure.[26,29] Lower the risk of getting dengue by protecting yourself from the mosquito bite by using clothes to cover as much of your body as possible. Use of mosquito nets, window screen, mosquito repellents, coils & vaporizers helps reduce exposure to the mosquitoes.

Patients who are at high risk of complications based on clinical assessment should be admitted in the hospital under intensive care and closely monitored. Fluid assessment and judicious replacement is vital to prevent shock state. Those who are not sick enough to warrant an admission should be observed in the community. Patient's education and counselling is very helpful.

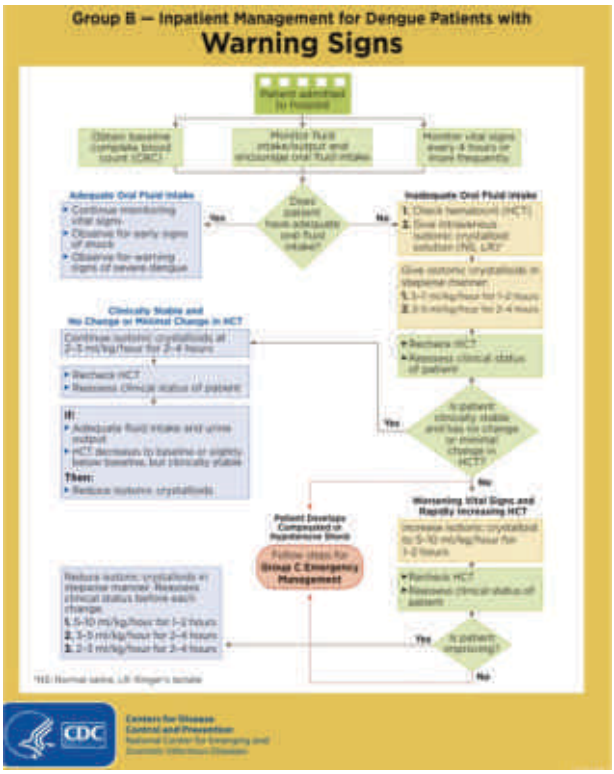

Table 2: *CDC Guideline for inpatient of Dengue Vitus Infection.*[31]

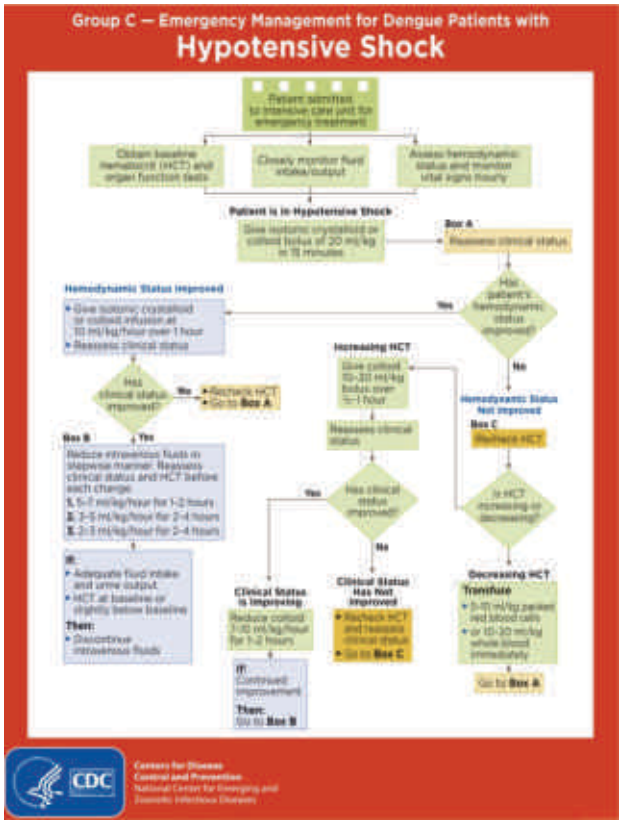

Table 4: *CDC Guideline for decompensated shock of Dengue Vitus Infection.*[31]

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References

1. Shepard DS, Undurraga EA, Halasa YA, et.al. The global economic burden of dengue: a systematic analysis. Lancet Infect. Dis. 2016: 16(8):935-41.
2. Centres for Disease control & prevention. 2014. CDC-epidemiology-dengue. Available from: [http:// www.cdc.gov/dengue/index.html].
3. Bhatt S, Gethung PW, Brady OJ. The global distribution & burden of dengue. Nature. 2013: 496(6446):504-7.
4. Byk LA, & Gamarnik AV. Properties & functions of the dengue virus capsid protein. Annu Rev Virol. 2016; 3(2): 263-81.
5. Carrington LB & Simmons CP. Human to mosquito transmission of dengue viruses. Front. Immunol. 2014: doi: 10.3389/fimmu.2014.00290
6. Chao CH, Wu WC, Lai YC. Dengue virus NS-1 protein activates platelets via Toll-like receptor 4, leading to thrombocytopenia & haemorrhage. PLoS Pathog. 2019: 15(4): e1007625.
7. Chareonsirisuthigul T, Kalayanarooj S, Ubol S. Dengue virus antibody dependent enhancement of infection upregulates the production of anti-inflammatory cytokines but suppresses anti-DENV free radical and pro-inflammatory cytokine production, in THP-1 cells. J Gen Virol. 2007: 88(2):365-373.
8. Diamond MS, Pierson TC. Molecular insight into Dengue virus pathogenesis & it's implications for disease control. Cell. 2015: 162(3):488-92.
9. Bozza FA, Cruz OG, Zagre SM, et. Al. Multiple cytokine profile from dengue patients: MIP-1beta &IFN-gamma as predictive factors for severity. BMC infect. Dis. 2008: 8(1):86.
10. Fisch W, Bartenschlager R. Exploitation of cellular pathway by Dengue virus. Curr. Opin. Microbiol. 2011: 14(4):470-5.
11. Kao YT, Lai M, Yu CY. How dengue virus circumvents innate immunity. Front Immunol. 2018; doi: 10.3389/fimmu.2018.02860.
12. Rothman AL, Ennis FA. Immunopathogenesis of dengue haemorrhagic fever. Virology. 1999; 257(1): 1-6.
13. Mueller,Dana, malaria & dengue fever, in Arjun S. Infectious disease emergencies, Emergencies New York. online edn. Oxford academic, 1 Nov. 2016.
14. Parul D,S, Taay KM. Concurrent malaria & dengue infections among febrile patients. Indian J Microbiol. 2017: 35(3): 7-9.
15. Arun KM, Nischal S, Sakar BG, Madhu S. Typhoid Fever among patients diagnosed with dengue fever in a tertiary care centre. A descriptive cross-sectional study. JNMA J Nepal Med Assoc. 2022: 60(252):714-7.
16. Amin Islam, Christopher C, Shereen E, Javeed A, Kevin J, et. al. Coagulopathy of Dengue & COVID-19: clinical considerations. Trop Med Infect Dis. 2022;7(9):210.
17. Henrina J, Puttra ICS, Lawrensia S, Handoyono QF, Cahyadi A. Coronavirus disease. A mimicker of dengue infection? SN Compr Clin Med. 2020: (2) 1109-19.
18. Centre for disease control & prevention (CDC). Is it a dengue or is it a COVID? Available online. [http:// www.cdc.gov/dengue/healthcare-providers/dengue-or-covid.html].
19. Waggoner JJ, Gresh L, Vargas MJ, Ballesteros G, Tellez Y, et al. Viremia & clinical presentation in Nicaraguan patients infected with Zika virus, chickengunya virus & dengue virus. Clin Infect Dis. 2016:63(6):1584-90.
20. Potts JA, Rothmann AI: clinical & laboratory features that distinguish dengue from other febrile illnesses in endemic population. Trop Med Int Health. 2008: 13(11): 1328-40.
21. Abhilash KPP, Jeevan JA, Mitra S, et al. Acute undifferentiated febrile illness in patients presenting to a tertiary care hospital in South India: clinical spectrum & outcome. J Global Infect. Dis. 2016;8(4):147-54.
22. Jain V, Chopra A, Mir Ka, Babu C, Kohli S, Kapur P, Manjavkar S. Clinico-biochemical differences of patients presenting with dengue & chickengunya during post monsoon season. J Clin Diagn. Res. 2018;12(3): OC01 -OC04.
23. Shah I, Katira A. Clinical & laboratory profile of dengue, leptospirosis and malaria in children: a study from Mumbai. Arch Dis Child. 2007;92(6):561.

24. Chrispal A, Boorugu H, Gopinath KG, et al. Acute undifferentiated febrile illness in adult hospitalised patients: the disease spectrum & diagnostic predictors-an experience from a tertiary care hospital in South India. Trop Doct. 2010;40(4):230-4.
25. Peeling RW, Artsob H, Pelegrino JL, Buchy P, Cardosa MJ, et al. Evaluation of diagnostic tests: Dengue Nat Rev Microbiol. 2010;8(S1): S30-S37.
26. WHO Dengue Guidelines for diagnosis, treatment, prevention & control: new edition available online. ISBN: 978 92 4 154787 1
27. Kellstein D, Fernandes L. Symptomatic treatment of dengue. Should the NSAID contraindication be reconsidered? Postgrad. Med. 2019;131(1):109-16.
28. Zapata JC, Cox D, Salvato MS. Role of platelets in the pathogenesis of viral haemorrhagic fevers. PLoS Negl Trop Dis. 2014;8(1):e2858.
29. Rajapakse S; de Silva, NL, Weeratumga P, Rodrigo C, Fernando SD, et al. Prophylactic & therapeutic interventions for bleeding in Dengue: A systematic review. Trans R Soc Trop Med Hyg. 2017;111(3):433-9.
30. Tayal A, Kabra SK, Lodhacorresponding R. Management of Dengue: An Updated Review. Indian J Pediatr. 2023; 90(2): 168–77.
31. CDC-Guidelines for clinicians re: management of dengue fever. Available from: [https://www.cdc.gov/dengue/resources/dengue-clinician-guide_508.pdf]