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CHAPTER 6

Clinical Presentation of Dengue Infection

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ABSTRACT

Four Flaviviridae family members, which are antigenically related strains of the dengue virus (DENV 1-4), are responsible for the arboviral disease dengue. The majority of dengue fever cases may progress unharmed. However when viral genetics and serotype-specific immunity interact, it can lead to a life-threatening disease in some patients. Asymptomatic dengue infection is one end of the infection spectrum, which also includes dengue shock syndrome (DSS), dengue fever (DF), dengue hemorrhagic fever (DHF), and undifferentiated febrile sickness (UF). It frequently develops suddenly and is accompanied by a sharp rise in body temperature, with headache, and a flushed appearance. It can also cause severe headaches, muscle, joint, and bone pains, also known as "bone breaking fever." Simple tourniquet tests help with early dengue infection identification. Increased vascular permeability, which leads to plasma leakage, decreased intravascular volume, and shock in extreme cases, is a hallmark of DHF. The plasma leakage is distinctive in that it only occurs in the pleural and peritoneal cavities. Usually only lasting 24–48 hours, this crucial time of leakage requires careful monitoring. Patients with symptoms are divided into two categories by the World Health Organisation: severe dengue and dengue with or without warning signs. Medical personnel can prioritise patients for hospital or intensive care admission using this subcategorization of dengue. With close monitoring and prompt treatment of patients with severe dengue, outcomes have improved.

INTRODUCTION

Dengue is an illness brought on by one of the four dengue viruses (DENVs), which are transmitted by *Aedes aegypti* or *Aedes albopictus* mosquitoes during a blood meal. The clinical manifestations of infection can range from being asymptomatic to having a wide range of clinical presentations, from the often mild febrile illness to the occasionally lethal shock syndrome.[1] The likelihood of infection and the severity of the disease are thought to be influenced by a variety of factors, including the virus, host, and vector. The likelihood of developing severe dengue sickness is influenced by the intricate interactions between viral genomes and population dynamics of serotype-specific immunity.[2]

The four Flavivirus variants DENV-1, DENV-2, DENV-3, and DENV-4 are serologically similar but not antigenically identical.[3] People who reside in dengue-endemic regions, where all four DENV varieties co-circulate, are consequently susceptible to infection from any

and all DENV varieties. Cross-protection between the four types exists momentarily, but it degrades and vanishes in the months that follow infection. Very serious infection is brought on by secondary infection with a different strain of dengue virus.[4] For clarity, consider that a patient may contract dengue four times in their lifetime, with each subsequent illness having the potential to be more severe.

CLASSIFICATION SCHEMES

The 1997 WHO Definition

The World Health Organization (WHO) proposed three categories of symptomatic DENV infection in 1997: dengue fever (DF), dengue hemorrhagic fever (DHF), and dengue shock syndrome (DSS). The term DHF emphasizes that shock and warning signals are caused by plasma leakage rather than hemorrhage, which is the main sign of severe dengue. Plasma leakage and serial hematocrit values are primarily the focus of clinical management recommendations and algorithms. Additionally, not all patients with serious illnesses requiring medical care meet the criteria for DHF. When the 1997 WHO criteria for DHF is applied, it is generally believed that the clinical impact of DENV infection is understated.[5]

The 2009 WHO Definition

A significant proportion of severe dengue cases with serious organ involvement were missed by the 1997 classification. In addition, there have been reports that the case definition of DHF is overly detailed and difficult to use in environments with limited resources. The 2009 clinical categorization was recommended as the new case definition.[6]

The WHO separated dengue into two main groups in 2009 depending on severity: severe dengue and dengue with or without warning signs. This updated approach of classification guarantees early triage based on warning symptoms, prompt treatment, and reduces the chance of developing severe dengue. Dengue with or without warning signals and severe dengue are the two main categories shown in Fig. 6.1.

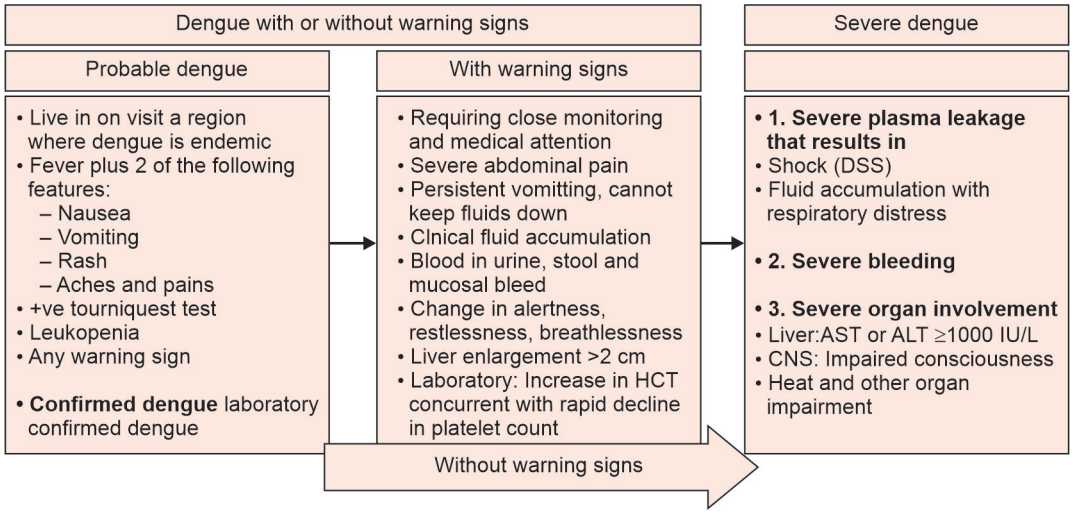

Fig. 6.1: Categorization of dengue infection

HCT: hematocrit; AST: aspartate transaminase; ALT: alanine transaminase; dengue infection is categorized as dengue with or without warning signs and severe dengue.

PATHOPHYSIOLOGY AND PATHOGENESIS

DHF happens in a tiny percentage of dengue patients. Most DHF cases include individuals who have a subsequent illness, sometimes referred to as a secondary infection. The pathophysiology of DHF is thought to be mediated by the immune system. Through antibody-dependent enhancement, there is a connection between secondary dengue infections and the start of DHF/DSS[7]. The aetiology of severe dengue is thought to be immune-mediated since severe clinical symptoms often arise when the virus load is sharply declining.[7,8] The innate and adaptive immune systems are also involved in this process. During a secondary infection, increased immunological activation results in an increased cytokine response. This changes the permeability of the blood vessels, which causes secondary dengue to present with severe symptoms.[9] Moreover, viral byproducts like NS1 may regulate complement activation and vascular permeability.

Increased vascular permeability resulting in plasma leakage, decreased intravascular volume, and shock in severe circumstances are characteristics of DHF. Plasma typically spills into the pleural and peritoneal cavities, and the leaking typically lasts just a short time (24–48 hours). Pleural and peritoneal inflammation is absent, and shock is quickly recovered from. Therefore, rather than structural endothelium damage, the primary mechanism appears to be functional alteration in vascular integrity. Only a few studies have shown that complement activation and DHF are brought on by the NS1 antigen of the dengue virus.[10] Additionally, studies have shown that compared to DF patients, those with DHF had higher viral loads.[11]

CLINICAL MANIFESTATIONS

Dengue virus infection can manifest in the form of asymptomatic dengue virus infection and symptomatic dengue virus infection. The symptomatic dengue virus infection includes undifferentiated febrile illness (UFI), dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS).[12]

The illness usually starts suddenly with fever following the incubation period and progresses through three stages, namely the febrile phase, critical phase, and recovery phase.

Febrile Phase

Fever: The body temperature is characteristically sudden onset and high-grade between 39 and 40°C. It can be biphasic, typically last 2–7 days.[13]

Rash: Over the first two to three days, the face, neck, and chest may experience diffuse flushing or brief eruptions. On the third or fourth day, a prominent rash, that may be maculopapular or rubelliform, emerges.[14] Some patients develop injected oropharynx and facial erythema in the first 24–48 hours. On the arms, hands, dorsum of the foot, and legs, little clusters of petechiae may occur. Usually, it vanishes just before or shortly after defervescence, towards the end of the feverish phase. This convalescent rash is characterised by confluent petechiae surrounding intermittent pale, circular areas of normal skin. During the period of recovery, skin may itch. This minor phase will pass on its own.

One may experience a severe headache, pain in the muscles, joints, and bones, retro-orbital eye pain, and a maculopapular or macular rash. Additional signs and symptoms that could exist include mild hemorrhagic manifestations like petechia, ecchymosis, purpura, epistaxis, bleeding gums, haematuria, or a positive tourniquet test result. The tourniquet test helps

with early dengue infection identification and can distinguish between dengue and other infections with overlapping symptoms.[15]

The appearance of abdominal pain, continuous vomiting, fluid buildup, mucosal bleeding, lethargy, enlarged liver, and increasing hematocrit with falling platelet count are early warning signals that appear at defervescence. Its occurrence suggests that a patient with this condition could develop severe dengue. Within a few hours, people who have significant plasma leakage as a result of markedly increased vascular permeability can get severe dengue and shock.

Critical Phase

The transition from the febrile to the afebrile phase, which occurs after 3–7 days of fever, signals the beginning of the critical phase of DHF. When the temperature is already dropping (below 38°C/100°F), a small percentage of patients may experience a sharp worsening of symptoms.[16] This important window lasts only 24–48 hours. There is plasma leakage during this time, and warning symptoms start to appear. Plasma leakage and warning symptoms are typically brought on by leukopenia and a sharp decline in platelet count.[17] DHF manifests as the critical phase of dengue and is characterised by abnormal hemostasis and selective plasma leakage in the abdominal and pleural cavities. Ascites, hypoproteinemia, haemoconcentration, pleural effusions, and ascites can all occur in patients with significant plasma leakage.

Initially, physiological compensatory mechanisms keep the circulation adequate, which causes the pulse pressure to narrow while the systolic blood pressure is maintained but the diastolic blood pressure rises. The pulse pressure is frequently narrow in dengue shock. Therefore, it is a challenging situation for the clinician because only looking at systolic pressure could miss a dengue shock scenario. Plasma loss causes substantial hypovolemic shock. Cold, clammy skin, a thready pulse, a constricted pulse pressure, shock, and fluid accumulation with respiratory difficulties are symptoms of severe plasma leakage.

Hematocrit rising by 10–15% above baseline is the first sign of the critical period. Prior to clinical detection of plasma leakage, radiography and ultrasound confirmation are required. A right lateral decubitus chest radiograph has greater sensitivity to detect pleural effusion. Gallbladder wall oedema, which may occur before a clinical diagnosis, can be visible as plasma leakage. A much lower serum albumin level than the initial value of >0.5 g/dl is indirect indication of plasma leakage.

Moderate to severe thrombocytopenia and concurrent hemoconcentration, indicated by increased hematocrit, are consistent laboratory results. A clinical diagnosis of DHF is most likely if there is significant plasma leakage and fever, even if there is no bleeding or thrombocytopenia.

Hemorrhagic complications, such as epistaxis, gingival bleeding, and polymenorrhea or menorrhagia, are common in dengue fever. Although rare, severe bleeding (DF with unusual hemorrhage) is an important cause of death in dengue fever. It includes hematuria, hemoptysis, gastrointestinal bleeding, and intracranial or subarachnoid bleed. Dengue fever with hemorrhagic manifestations must be discriminated from dengue hemorrhagic fever which has significant plasma leakage and no hemorrhage. Patients who have considerable bleeding or plasma leakage may develop dengue shock syndrome. In particular, most patients maintain consciousness practically all the way until the end. If prompt, effective therapy with volume replacement is provided, shock can be reversed. However, if adequate care is not provided at this stage, mortality follows in shock patients.

Apart from intravascular hypovolemia and shock, various additional specific cardiac manifestations have been described, ranging from the rare fulminant myocarditis to the more common functional myocardial impairment and arrhythmias.[18]

A more complicated course with metabolic acidosis and electrolyte imbalance, multiorgan failure, and severe bleeding may ensue in patients with extended or untreated shock. Severe dengue is the name given to it. Hepatic and renal failure are typically observed in prolonged shock, which can result in electrolyte imbalances and metabolic encephalopathy. The prognosis is poor and the mortality rate is significant in an extended or untreated shock.[19]

Patients with dengue shock need to be closely watched since it might take just a few hours from the time warning signals appear to the onset of compensated shock and hypotensive shock.[20] The time between hypotensive shock, cardiorespiratory collapse, and cardiac arrest may just be a few minutes, thus the doctor must be careful. Clinicians must act quickly to intervene in order to prevent the progression of dengue compensated shock to hypotensive shock. The variations between the compensated and hypotensive shock groups of dengue shock are shown in Table. 6.1.

Table 6.1: Variations in compensated shock and hypotensive shock groups

Hemodynamic parameters	***Compensated shock***	***Hypotensive shock***
Physiology	Body compensates to maintain blood pressure	Perfusion of vital organs not maintained
Conscious level	Clear and lucid	Agitated and aggressive
Capillary refill	Prolonged (>2 sec)	Very prolonged, mottled skin
Extremities	Cool peripheries	Cold, clammy
Peripheral pulse volume	Weak and thready	Feeble or absent
Heart rate	Tachycardia for age	Severe tachycardia or bradycardia in late shock
Blood pressure	• Normal systolic pressure, but rising diastolic pressure • Narrowing pulse pressure • Postural hypotension	• Narrow pulse pressure (<20 mm Hg) • Hypotension • Unrecordable blood pressure
Respiratory rate	Tachypnea	Hyperpnea or Kussmaul's breathing (metabolic acidosis)
Urine output	Reducing trend	Oliguria or anuria

Recovery Phase

The patient enters the recovery or convalescent phase as the plasma leakage slows down and starts to reabsorb extravasated intravenous fluids as well as pleural and abdominal effusions. Diuresis and an increase in appetite are indicators that the body is healing and that volume replacement should stop. Hemodynamic state stabilises when the patient's condition gets better, and diuresis follows. Due to the dilutional effect of the reabsorbed fluid, the patient's hematocrit stabilises or may even decrease, and the white cell count typically starts to climb. Next, the patient's platelet count recovers. The doctor must make a critical decision at this point about whether the patient's fluid needs will decrease or, in rare cases, whether excessive fluid delivery would result in fluid overload.

Expanded Dengue Syndrome

Expanded dengue syndrome refers to the unique appearance of people with extensive organ involvement, such as the liver, kidneys, brain, or heart, in both DHF and in dengue patients without evident plasma leakage. These odd manifestations may result from co-occurring illnesses, co-morbid conditions, or long-lasting shock-related adverse effects.

DIAGNOSIS OF DENGUE AND DENGUE HEMORRHAGIC FEVER

Numerous pathogens or disease states mimic the spectrum of illnesses brought on by dengue infection. Accurate clinical diagnosis of dengue is exceedingly challenging, and diagnosis can be overlooked very easily because of the wide variety and similarity of its clinical signs. Therefore, it is crucial to combine the evaluation of clinical presentation with the use of laboratory and point-of-care diagnostics.

Clinically, the diagnosis of dengue is made highly likely in any patient who presents with a febrile illness and has two or more symptoms, including a headache, retro-orbital pain, myalgia, arthralgias, bone aches, rash, and signs of leucopenia, thrombocytopenia, and rising hematocrit. The presence of IgM antibodies against the dengue virus and the detection of NS-1 antigen (rapid diagnostic test) are used to confirm the diagnosis.[21]

Since it is secreted by infected cells, the viral protein NS1 (non-structural protein 1) is present in high circulating levels in the blood of infected people. At the onset of clinical symptoms in primary dengue infection, NS1 antigen is present in the serum of infected individuals and causes a potent humoral response. It can be found before IgM antibodies start to show up. The window of detection for NS1 can become smaller due to immunological complex development during subsequent infections. It serves as a stand-in for a viremia marker, and research has revealed a correlation between viral titre and NS1 antigen levels [22,23]. However, it has been demonstrated that combining NS1 detection with IgM and/or IgG detection significantly enhances the diagnosis of dengue infection.

Anti-dengue IgM antibody develops a little sooner than IgG antibody does, and is often evident by day five of the sickness, meaning that the antibody is typically not noticeable for the first five days of the disease. IgM antibody does not emerge at the same time in all patients, though. Although IgM titers of 320 are frequently attained in cases of secondary infections, IgM antibody titers in primary infections are significantly higher than those in secondary infections. Detectable IgM may persist in certain primary infections for longer than 90 days, although in the majority of patients, it declines to undetectable levels by 60 days. However, the presence of IgG antibodies against the dengue virus suggests a history ofn infection.

To differentiate between primary and secondary dengue infection, researchers employ the IgM/IgG ratio. If the capture IgM/IgG ratio is larger than 1.2 or lower than 1.2, a dengue virus infection is classified as primary, and as secondary, respectively. [24]

Rapid diagnostic tests are crucial in practise since many serum samples are obtained during the first five days of the onset of the illness and do not contain detectable IgM antibodies. For the purpose of identifying DENV infection, molecular techniques like RT-PCR and nucleic acid hybridization have been effective. When the disease is acute, DENV can be diagnosed the same day or the day after using PCR-based techniques. Viral RNA can be detected using PCR-based techniques from the first signs of sickness, and they are more accurate, swift, simple, and affordable than virus isolation approaches.[25]

The timing of dengue biomarker emergence in patients with primary and secondary infections is shown in Fig. 6.2. In primary infection (Fig. 6.2A), both the NS1 antigen and the

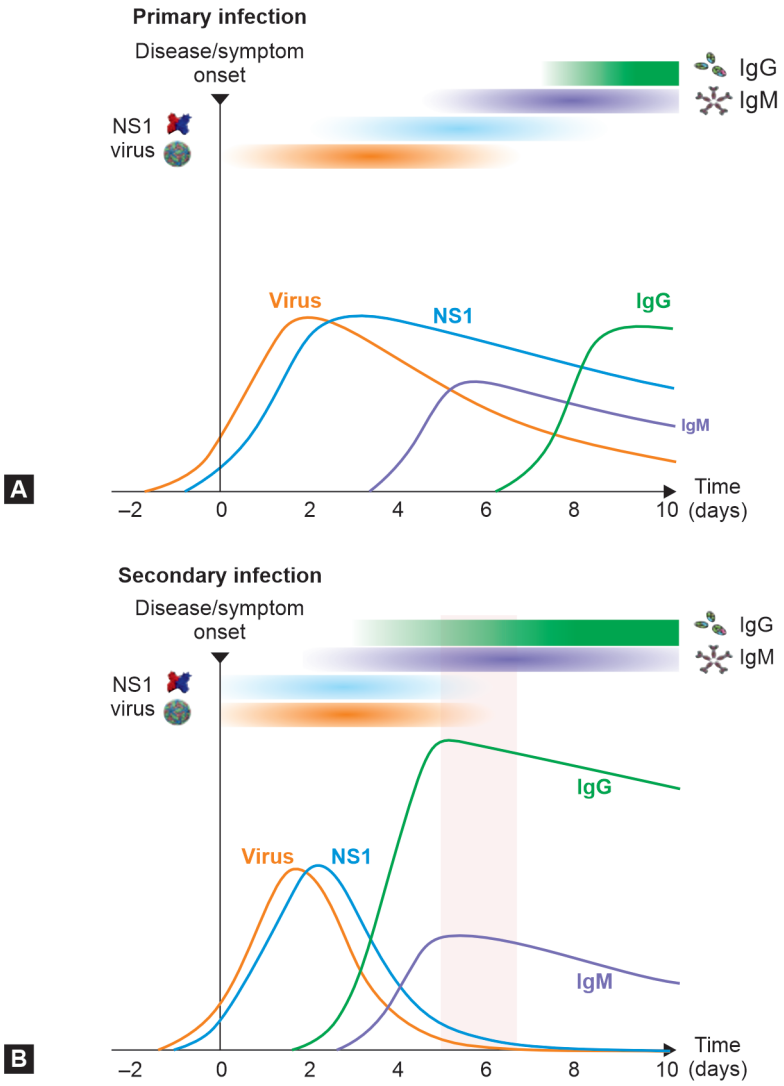

Fig. 6.2: Timeline of dengue biomarkers in primary and secondary dengue

virus can be seen before symptoms develop. Immunoglobulin M (IgM) and immunoglobulin G (IgG) arrive at different times during the acute phase of the illness. The appearance of IgG early in the acute phase of the disease and a shorter duration of NS1 and viral detection are characteristics of secondary infections (Fig. 6.2B). It is important to take note of the start of severe dengue (dengue hemorrhagic fever [DHF]/dengue shock syndrome [DSS]), which typically occurs in secondary infections and when virus and NS1 levels are declining.

LABORATORY INVESTIGATIONS

The white blood cell (WBC) count may be normal or primarily neutrophilic during the early febrile period. The total quantity of neutrophils and WBCs then declines, reaching a low point towards the conclusion of the feverish phase. According to studies, the subgroups of DHF and dengue fever both exhibit minor and comparable liver enzyme derangements, and platelet and white-cell counts are much lower in DHF than in dengue fever. [26] Additional findings

include moderate albuminuria, prolonged partial thromboplastin time and prothrombin time, as well as hyponatremia in DHF that worsens as shock progresses. After accounting for hypoalbuminemia, hypocalcemia has been detected in every case of DHF. Once in shock, patients frequently exhibit metabolic acidosis, and their blood urea nitrogen levels are higher in prolonged shock. Aspartate transaminase (AST) and alanine transaminase (ALT) are frequently elevated, with AST increasing significantly more than ALT as in alcoholic hepatitis. An increase in amylase and lipase levels is not unusual in dengue fever, especially if the patient has ongoing abdominal pain.

COMPLICATIONS OF DHF

These often go hand in hand with severe and prolonged shock, which can lead to metabolic acidosis, severe bleeding, and multiorgan failure, including hepatic and renal dysfunction. More importantly, excessive fluid replacement during the plasma leakage stage leads to large effusions that may impair breathing, result in acute pulmonary congestion, or even result in heart failure. If fluid therapy is continued after the plasma leakage period, it may cause acute pulmonary oedema or heart failure, especially if extravasated fluid is reabsorbed during the recovery stage. Additionally, severe/prolonged shock, ineffective fluid therapy, and electrolyte disruption can all lead to metabolic/electrolyte disruption. Common symptoms of metabolic abnormalities include hypoglycemia, hyponatremia, hypocalcemia, and on rare instances, hyperglycemia. These disturbances may cause a variety of strange symptoms, including encephalopathy.

Patients at High Risk

When caring for elderly, obese, pregnant, or patients with multiple co-morbid conditions like diabetes mellitus, hypertension, asthma, ischemic heart disease, chronic renal failure, and liver cirrhosis, one must use caution because the following host factors play a role in more serious disease and associated sequelae.

Ischemic Hepatitis/Failure

Acute liver failure, which can be fatal, can occasionally result from liver involvement in acute dengue infection. DSS may be accompanied by ischemic hepatitis, also known as hypoxia hepatitis or shock liver. Hepatic dysfunction is hypothesised to be caused by a number of factors, including immune-mediated harm, direct viral damage, and hypoxia injury from reduced perfusion. As a result, patients with dengue infection have higher levels of AST, ALT, and gamma glutamyl transferase (GGT) during the duration of their illness. On days 5 and 6, patients with severe dengue (SD) have significantly higher AST and GGT levels than do patients with non-severe dengue (NSD), with day 6 seeing the highest AST values. A large majority of dengue virus patients have high AST, ALT, and GGT values over the duration of their illness, with an AST:ALT ratio greater than 2. In patients with dengue-induced severe hepatitis, a high mortality dengue complication, the MELD score is the best indicator of acute liver failure.

Acute Renal Failure

Acute kidney injury develops in severe dengue as a result of decreased effective circulatory volume brought on by plasma leakage. The fluid treatment can typically fix this. Nevertheless, depending on each person's needs, it might necessitate diuretics or renal replacement therapy.

Management of Severe Haemorrhage

If the cause of the bleeding is found, efforts should be made to stop it if at all possible. Nasal packing, for instance, may be used to control severe epistaxis. Lifesaving blood transfusions should never be postponed until the hematocrit is dangerously low. This needs to be refilled if blood loss can be measured. Nevertheless, aliquots of 10 ml/kg of fresh whole blood or 5 ml/kg of freshly packed red cells should be transfused and response assessed if this cannot be quantified.

H-2 antagonists and proton pump inhibitors have been used to treat gastrointestinal bleeding, but no studies have been done to demonstrate their effectiveness. The use of blood components such platelet concentrates, fresh frozen plasma, or cryoprecipitate is not supported by any data. Its use could result in fluid overload. Recombinant Factor 7 however might be useful in some individuals without organ failure.

Management of High-risk Patients

Because obese patients have diminished respiratory reserves, it is important to avoid giving them too much intravenous fluid. Colloids should be taken into account in the initial stages of fluid therapy, and fluid replacement and resuscitation should be calculated using the optimal body weight.

In order to manage blood sugar levels in dengue patients with diabetes mellitus, intravenous insulin is typically required. It is best to use crystalloids devoid of glucose.

Early admission of dengue-infected pregnant women allows for rigorous disease monitoring. It is crucial to have multidisciplinary team treatment from the obstetrician, physician, and paediatrician. In serious cases, families may need to receive detailed advice from all angles. When using pre-pregnancy weight as a computation, the amount and rate of IV fluid for pregnant women are typically comparable to those for non-pregnant women.

Anti-hypertensive medications given to patients with hypertension may conceal the cardiovascular response to shock. It is important to take into account the patient's individual resting blood pressure. For certain patients, a blood pressure that appears to be normal may actually be low.

During the critical period, anticoagulant medication may need to be temporarily stopped.

Hemolytic Diseases and Haemoglobinopathies

These individuals frequently need blood transfusions and are at risk of hemolysis. Alkalinization therapy and hyperhydration should be avoided because they can cause fluid overload and hypocalcemia. Fluid therapy should be administered with caution because their cardiac reserves may be lower.

It is advised for patients receiving steroid medication to continue receiving it.

CONCLUSION

After learning all the fundamental concepts, advantages, and disadvantages of fluid treatment, treating dengue patients is an art. Patients with dengue come with a variety of clinical manifestations. The important components in the therapy of dengue patients are the identification of warning signals and hydration.

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