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Current Review

Optimising Management in Dengue: Current Concepts and Challenges

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A B S T R A C T

Around 96 million cases of dengue have been reported worldwide in tropical and subtropical countries. It has increasingly become a public menace. Fluid resuscitation, though the mainstay of treatment, is associated with various concerns faced by clinicians. The major issues include the choice of fluid-crystalloids versus colloids, when to use inotropes, and the role of blood and blood components in clinical practice. Point of care ultrasound has newly come up as a non-invasive modality for the assessment of fluid status in dengue. This narrative review article addresses the current concepts and challenges faced by clinicians during the management of dengue disease.

Keywords: Dengue, Management, Current Concepts, Fluid Therapy, Ultrasound

Introduction

The clinical spectrum of dengue varies from mild febrile illness to serious bleeding and shock. With the earliest reports dating back to the 1950s from countries like Thailand and the Philippines, the disease has become a major cause of hospitalisations and deaths in tropical countries and with the nations of the developed world, though 70% of the burden is still from Asia.[1] Not only has the disease become endemic over large geographical regions of the world, but major outbreaks are also reported every year across the globe. With the current pandemic of COVID-19, several countries have faced major outbreaks of dengue as well, including northern India still facing the dual brunt on health services.

Dengue comprises three phases, i.e., febrile, critical, and recovery, with the critical phase heralding the onset of capillary leakage. This corresponds to a rise in haematocrit and a fall in platelet counts causing dengue shock and bleeding tendencies, leading to significant morbidity and mortality.[2,3] Untreated dengue can have mortality as high as 20%, however appropriate and timely management can reduce these figures to less than 1%. Despite a better understanding of pathophysiology, the treatment of dengue disease spectrum remains challenging due to its unpredictable course.

Evolution of Classification System of Dengue

Dengue fever (DF) and Dengue Haemorrhagic Fever (DHF)/Dengue Shock Syndrome (DSS) are the two major entities as per the World Health Organization (WHO). This classification was developed on the basis of research in a paediatric population in Southeast Asia. The classification of severity was done on the basis of peculiar symptoms and signs. The traditional classification demands the fulfilment of four criteria for inclusion as a case of DHF, however, there were conditions where all four criteria were not observed, leading to problems with the classification of severe cases. Several researchers have mentioned problems encountered in accommodating the traditional classification

in order to document clinical cases of dengue, for example, haemorrhagic manifestations,[4] thrombocytopenia,[5,6] and fluid leakage.[4,5] Though the traditional classification is widely recognised for its advantages, the need for alternative criteria for defining the clinical spectrum became the need of the hour owing to the complexities of the traditional system.[7,8] Bandyopadhyay[9] via a multicentric study proposed that modification of the traditional WHO classification is imperative. Alexander et al. conducted a multicentric study in Latin America and Asia during the period from 2006 to 2007 which led to a revised proposal for dengue classification.[10] The new classification system (2009) classified dengue into three severity categories needing three levels of care. Category III comprised patients with a severe condition and included cases with severe haemorrhage, profound shock, and multisystem involvement. Further, WHO revised the classification system which was also adopted by the National Vector Borne Disease Control Program (NVBDCP) in 2020. It classified dengue into mild, moderate, and severe categories on the basis of clinical severity and described management accordingly.[11]

This constantly evolving classification system often causes a dilemma among clinicians and researchers, not only in individual patient management, but also while extrapolating results of previously conducted studies on patients classified with the current system.

Management Concerns in Dengue

The mainstay of management of dengue illness is adequate fluid resuscitation, depending upon the phase of illness. Mild cases required only supportive and symptomatic treatment. These patients who have minimal plasma leakage recover without any complication with adequate oral intake. Patients with moderate to severe plasma leakage and without adequate oral intake would require hospital admission and appropriate intravenous fluid therapy. Fluid therapy is guided by the haematocrit values, which show an increase in plasma leakage. However, it is noteworthy that after the critical period, extravasated fluid is reabsorbed into the circulation, putting the patient at risk of fluid overload.[11,12]

Challenges in Clinical Assessment

Delayed Detection of Plasma Leakage: Critical phase begins with a capillary leak but clinically it may not be evident until a significant amount of plasma extravasates from the intravascular to the extravascular compartment. Repeating haematocrit, chest X-ray, serial monitoring of serum albumin levels, and USG by trained personnel are the simplest methods for detection of plasma leakage in uncomplicated cases. Tachycardia is an early and sensitive indicator of intravascular volume depletion but confounding factors like fever, anxiety, pain etc preclude its use as a diagnostic marker of plasma leakage in a dengue patient.

Inaccurate Clinical Assessment: Signs of capillary leakage are subtle in the beginning and may be missed easily. Moreover, the peri-orbital puffiness and ascites may mask the signs of dehydration and patients may appear fluid overloaded despite low intravascular volume.

Central Venous Pressure (CVP) Monitoring: CVP monitoring is considered the gold standard to measure intravascular fluid volume. However, critically sick patients of dengue invariably have severe thrombocytopenia and it becomes difficult to obtain central venous access due to the risk of bleeding.

Multifactorial Shock: Though plasma leakage is the main mechanism thought to be the reason for shock in dengue patients, it is not the only factor responsible. Shock in dengue can be multifactorial. Dengue illness may directly involve the myocardium and cause cardiogenic shock. Severe cytokine storm in a patient with dengue can lead to vasodilatation and septic shock. Massive collection of fluid in pleural and pericardial cavities can also lead to obstructive shock. The approach and management of shock in a particular patient need to be individualised.

Challenges during Fluid Therapy

Choice of Intravenous Fluid

The two primary kinds of volume expanders that are utilised to replace the lost fluid to manage dengue fever are crystalloid and colloids.[2] Normal saline, an isotonic solution having an osmolality of 308 mOsm/L, with greater sodium and chloride concentration than that in normal plasma, is the most commonly used crystalloid. For initial fluid resuscitation, normal saline should be used but it may lead to hyperchloremic acidosis if its repeated large volume is used. Although Ringer lactate has low sodium and chloride with an osmolality of 273 mOSm/L, but it is not advised in cases of liver failure because the capacity to metabolise lactate is reduced. Dextran, gelatin, and starch-based solutions are the usual colloids that are utilised for plasma volume support.[13,14] For emergency resuscitation in case of hypovolaemic shock, sometimes colloids are preferred over crystalloid solutions as they can increase volume more than the actual volume administered. In clinical practice, however, there is not much difference in outcome when crystalloids or colloids are used. Several randomised controlled trials have compared the different types of fluids in severe dengue cases but no conclusive evidence can be drawn in favour of either type of fluid (Table 1).[15-18]

However, heterogeneity and lack of studies in severe dengue with and without shock make it difficult to interpret the results. One systematic review conducted in the year 2015 concluded crystalloids to be as effective as colloids with the available evidence.[19]

Table 1.Summary of Randomised Controlled Trials Comparing Crystalloids and Colloids in Dengue

Study	Age Group (Years)	Sample Size	Fluids Compared	Outcome
Bridget et al.[15]	2-15	383	RL 6% Dextran 6% HES	The patient treated with RL took longer for cardiovascular stabilisation than the patient receiving colloid. However, no difference was observed in the primary outcome measures of shock reversal.
Ngo et al.[16]	1-15	230	RL NS Dextran 3% Gelatin	No statistically significant difference was observed between crystalloid and colloid.
Kalayanarooj et al.[17]	2-15	104	Dextran 40 10% Haes-steril	No statistically significant difference was observed between crystalloid and colloid.
Dung et al.[18]	5-15	50	RL NS Dextran 70 3% Gelatin	Dextran 70 was found to be most effective for the improvement of cardiac index and haematocrit, but the study has a very small sample size.

Fluid Overload Management

Fluid overload is the most dreadful complication during dengue management. If not managed properly and timely, it may lead to heart failure, acute pulmonary oedema or even death. Resorption of fluid back into intravascular space from extravascular space during the recovery phase and unregulated fluid therapy, both may lead to significant fluid overload requiring urgent medical intervention. A recovering patient presenting with tachycardia, tachypnoea, liver enragement, and breathing difficulty should be suspected to be in fluid overload. Diuretics have shown to be beneficial in cases of pulmonary oedema where they significantly improve oxygenation parameters. However, using them in patients with active capillary leakage can further worsen intravascular hypovolemia. Thus one has to be extra cautious while using them. Refractory fluid overload can be managed primarily with continuous renal replacement therapy, which has added advantage over haemodialysis as it is known to cause less haemodynamic instability.[20]

Inotropes in Dengue Management

There is a paucity of clinical literature regarding the role of different inotropes and vasopressor agents in dengue shock, and which among these is preferred over the other and why. The common consensus is to treat dengue shock as a hypovolemic shock which if refractory to intravenous fluid therapy, the treatment should immediately switch over to inotropic support along with fluid therapy. If cardiac dysfunction is suspected, then dobutamine is preferred as first-line inotropic support. However, current clinical evidence are not enough to make any recommendation.[21]

Blood and Blood Components in Dengue

The need for transfusion of blood and platelets is widely accepted and practised in clinical settings of dengue. The concern with blood transfusion is the interpretation of haematocrit. A fall in haematocrit may occur as a result of improvement in the capillary leak or fluid resuscitation or contrarily due to bleeding in the patient. Broadly, a fall in haematocrit, in presence of active bleeding should be an indication of blood transfusion with a strict vigilance on signs of fluid overload. Though no randomised trials could be found comparing blood transfusion practices in dengue, unwarranted transfusions against WHO recommendations were shown to increase the time and cost of hospitalisation in adult patients from Brazil.[22] Also, it increases the risk of fluid overload and adverse reactions associated with transfusions.

Similarly, indications and timing of platelet transfusion is also varied in clinical practice and lacks substantial evidence. Transfusion of platelets is mostly suggested if the platelet count is less than 10,000/µL without bleeding or at higher values if active bleeding is there. A large multicentric trial was conducted over five countries comparing prophylactic platelet transfusion along with supportive care with only supportive care in patients above 21 years of age. Prophylactic platelet transfusion at a cut-off of 20,000/µL was not found to be superior in preventing active bleeding in this large cohort of patients.[23] In absence of randomised trials due to ethical concerns in conducting them, judicious use of platelet transfusions should be done in clinical practice, with regular monitoring.

As dengue may also have coagulopathy with bleeding, fresh

frozen plasma or cryoprecipitate may be given guided by the clinical condition of the patient, keeping in mind the fluid status.

Role of Steroids

The addition of short-course steroids in the early phase of dengue illness owing to dysregulated immune response was evaluated in a few studies till early 2000s. Four studies enrolling 664 children and adults from India, Columbia, Vietnam, and Sri Lanka performed the basis of Cochrane review and meta-analysis conducted in the years 2014 and 2015. The evidence does not support any benefit of corticosteroids in terms of mean hospital days, need for blood transfusion, pulmonary bleed, and seizures. With the current evidence, steroids should not be considered as a treatment modality in children with dengue.[19,24]

Point of Care Ultrasound to Diagnose and Manage Dengue

One of the most important challenges for clinicians while managing dengue cases is to find out and triage the patient showing early signs of plasma leakage. Overzealous use of fluid therapy in such patients is bound to lead to fluid overload situations which make the management more complex. The currently available biomarkers like Troponin T, pro BNP etc are not readily available in resource-limited settings.[25] Serial hematocritis sometimes less reliable due to individual variations, intravenous fluid therapy, bleeding, lab errors etc. Radiological parameters can be used as an alternative for the evaluation of plasma leakage (ascites and pleural effusion), but they have their limitations. Chest X-rays are able to detect only significant pleural effusions. In the early stage of illness, bedside ultrasonography has shown high sensitivity in predicting severe dengue infections.[26] It can detect even small amounts of pleural effusion and ascites in patients. Gall bladder thickening with honeycomb pattern is considered as one of the most peculiar signs in early diagnosis and in predicting the prognosis of severe dengue infection.[27-29] Ultrasound can be utilised as a less expensive and non-invasive technique that can be performed with minimal training.

A retrospective hospital-based study done by Pothapregada et al. revealed the importance of USG in case of children suffering from dengue fever along with its need in the analysis of the severity of the disease. They enrolled 254 children who were admitted with dengue fever. They were categorised as severe (62.6%) and non-severe (37.4%) cases. All the children were investigated with an ultrasonogram performed once during severe illness and again at discharge. About 156 subjects (61.4%) showed positive findings during the critical period of illness. Univariate analysis showed pericardial effusion, pleural effusion, ascites, peri-cholecystic fluid, gall bladder wall thickening, splenomegaly and hepatomegaly as the common findings seen in severe dengue infections. Among these, thickening of the gall bladder showed significant association with severe thrombocytopenia and was found to be the most specific sign. The resolution of these USG findings coincided with the clinical improvement.[30]

Bala subramanian et al. compared ultrasonography and chest radiography with clinical and laboratory signs of plasma leakage in predicting the early signs of plasma leakage. They established that USG is the most appropriate technique for screening DHF with a sensitivity of 91.42% and a negative predictive value of 82.41%.[31]

In another prospective study, the relationship between DHF and sonographic findings were studied. The study had enrolled 73 cases as mild (grades I-II) and 75 cases as severe (grades III-IV) and concluded that USG may be advantageous for early detection of the severity of DHF in children.[32]

With the evolution of cardiac protocols for detection of haemodynamic parameters in circulatory shock in different conditions, inferior vena cava measurement and its collapsibility index seems a useful option in dengue as well. An observational study in adults with dengue showed the advantages of dynamic monitoring of haemodynamic parameters using IVC measurement by USG in guiding fluid therapy and reducing complications.[33] A study from India has shown a good correlation between IVC collapsibility and high packed cell volume (PCV) and dengue shock among children with dengue.[34]

Recently, a correlation of IVC/aorta ratio with haematocrit and severity of dengue was evaluated among children with dengue. The authors reported IVC/Ao ratio < 0.8 to be significantly correlated with higher haematocrits for age, though associated with higher inter and intra-observer variation.[35]

Though scattered evidence, IVC measurements should be explored further in children with dengue as it seems to be a viable option for guiding fluid therapy in the rapidly changing and unpredictable haemodynamics of dengue illness spectrum.

Conclusion

Dengue fever continues to be a major health problem with significant morbidity and mortality. Owing to the lack of a specific treatment, supportive treatment with appropriate fluid therapy is the cornerstone of dengue management. However, dengue illness presents with multiple challenges and treatment needs to be individualised. Newer guidelines with clinical assessment-based titration of fluids seem to be more appropriate at present. Ultrasonography can prove to be a useful adjunct in monitoring dengue patients but availability and trained staff could be an issue.

Authors' Contributions

PA, VB and PB conceived the idea. PA and VB searched the literature and drafted the manuscript. The manuscript was critically reviewed and approved by all the authors. PB shall act as the guarantor.

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