F1000 MEDICINE REPORTS

Published: 28 September 2009
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Assessing the prognosis of dengue-infected patients

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F1000 Medicine Reports 2009, **1**:73 (doi:10.3410/M1-73)

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Abstract

Dengue infections pose a huge burden to health care providers in most tropical countries. Careful clinical examination and history-taking supplemented by newer rapid diagnostic tests may lead to early etiological diagnosis. For severe dengue, early recognition of vascular permeability followed by rapid physiological replacement of fluids is life-saving. Prognosis of patients depends upon optimum management, an outcome that requires preparation via organization, training, and use of evidence-based practice guidelines.

Introduction and context

The world is in the grip of a dengue pandemic heralded in 1977 by the emergence of each of the four dengue viruses from Asia to the Americas [1]. Until this pandemic is controlled, millions of patients with acute dengue illnesses will require diagnosis and treatment each year. Dengue viruses, members of the *Flavivirus* genus, are transmitted in an urban cycle, the virus traveling from viremic humans to mosquitoes (usually *Aedes aegypti*) and then to susceptible humans, generating a complex of syndromes – most of which are benign and short-lived but some with a fatal outcome – that is uniquely treatable. Prognosis is determined by an ill-understood combination of viral, immunological, and host factors, all of which begin with the sudden onset of high fever. There are no early signs that make it possible to predict severe outcomes, which only appear late and are accompanied by defervescence. It is critical that physicians who monitor dengue illnesses stay alert to the onset of the unique syndrome: dengue vasculopathy (dengue hemorrhagic fever [DHF]/dengue shock syndrome [DSS]). With the onset of this syndrome, prognosis rests squarely in the hands and prepared mind of the physician. Here, we will describe clinical features of severe dengue syndromes and outline treatment options where these are known to affect outcome.

Recent advances

Each of the four dengue viruses produces an acute febrile exanthema, which in its classic form (dengue fever) presents with an acute onset of fever, sometimes with shaking chills, and often with a retro-orbital headache. The disease may exhibit an early macular blush, conjunctival injection, myalgia, inappetence (including taste aberrations), upper respiratory signs, gastro-intestinal disturbances, and prostration. Patients often complain of the severity of their illness; prostration and weakness may extend well into convalescence. During infection, dengue viruses infect liver parenchyma and cells of the reticuloendothelial system. The febrile period lasts 4 or 5 days and is followed by defervescence and often a maculopapular generalized body rash. At defervescence, the disease will reveal its severe or relatively benign nature.

Severe dengue

Severe dengue is heralded by persistent vomiting, severe abdominal pain, extreme lethargy/weakness, mucosal bleeding, and (as a result of rapid plasma leakage) a rapid rise in hematocrit (HCT). Recognition of these warning signs should alert a prepared and rehearsed treatment team. In children, the predominant presentation often consists of a history of several days of fever with sudden signs of blood volume loss, tachycardia,

weak or thready pulse, skin that is cool to the touch, slow capillary filling, and decreased urine output. This state may progress to cyanosis, confusion, lethargy, and frank hypotension. The underlying mechanism is a rapid opening of putative 'capillary pores' that leak fluid and, in more severe cases, smaller proteins such as albumin into interstitial spaces. From this point onwards, patients who do not receive prompt intravenous fluid therapy may progress rapidly to a shock state, the outcome of which is time-sensitive. It is critical to recognize that shock presents as a continuum progressing from mild to moderate and severe hemodynamic instability. In the early phase of shock, the systolic blood pressure is maintained at the expense of increasing tachycardia and peripheral vasoconstriction, a state known as compensated shock. In dengue, this is manifested by narrow pulse pressure (less than 20 mm Hg); a systolic hypotension portends decompensation and an imminent total cardio-respiratory collapse [2]. Laboratory tests usually document a leucopenia characterized by neutropenia, mild to moderate elevations in liver enzyme blood values, and mild to moderate thrombocytopenia. Laboratory results do not accurately predict the hemorrhagic diathesis that often accompanies dengue infection; menstruating women may suffer menometrorrhagia, and individuals with peptic ulcer disease may experience a severe and potentially fatal gastrointestinal hemorrhage [3,4].

Management strategy

There are many parameters that can be deranged in severe dengue: thrombocytopenia, coagulopthy, hyperglycemia, liver enzymes, and multi-organ failure, all of which can distract the doctor's attention. In modern medicine, specialists may be called in for organ management: an anaesthetist for respiratory distress, a hepatologist for raised liver enzymes, a nephrologist for no urine output, a renologist for metabolic acidosis, a gastroenterologist for gastrointestinal bleeding, a neurologist for seizures, a hematologist for low platelets and coagulation defects, an endocrinologist for hyperglycemia, and a cardiologist for hypotension. The reason for multi-organ involvement is mainly (but not wholly) hypoperfusion. Specialty consults must not distract the physician in charge from focusing on one thing and only one thing: achieving and maintaining hemodynamic stability by fluid, colloid, or blood administration (without overloading the patient with too much fluid) until he or she is out of the critical period. All other clinical issues should await achievement of hemodynamic stability. Although patients with vascular permeability are resuscitated as if they have diarrhea, a more apt therapeutic analogy may be a burn injury or hypovolemia from 'third space' loss in surgery [5].

Treatment of dengue vasculopathy

Successful management of dengue vasculopathy relies on meticulous regulation of parenteral fluids and colloid during the period of increased vascular leakage, together with proactive management of major bleeding should this develop [6,7]. The physician should remember that in a 'leaky' capillary scenario, beyond a certain hydrostatic pressure, the faster the fluids are infused, the faster they leak into the 'third space', and that all fluid administered will be reabsorbed and fluid overload may result. Although vascular permeability is often thought to characterize severe dengue infections in children, it also occurs in adults [8]. Studies have shown that children are at higher risk than adults for developing vascular permeability during secondary dengue infections [9]. Placing the microHCT centrifuge on the ward for use by trained nurses facilitates the use of HCT determinations to manage fluid requirements and administration. Careful clinical research has provided invaluable data on which to base management guidelines [10-15].

From a double-blind randomized comparison of three fluids for initial resuscitation of 383 Vietnamese children with dengue shock, it was demonstrated that Ringer's lactate solution is sufficient to resuscitate children with moderately severe DSS [15]. However, should the disease proceed to severe shock, administration of dextran 70 or 6% hydoxyethyl starch will stabilize vascular volume and blood pressure in most cases. Given adverse reactions associated with the use of dextran, starch may be preferable for this group, although dextran 1 can be administered immediately before dextran 40 or 70, acting as a hapten inhibitor that blocks molecules of dextran 40 or 70 from forming toxic immune complexes [16]. A randomized controlled trial in children with dengue shock showed that aggressive intravenous fluid resuscitation in the first hour achieved 100% survival regardless of what fluid was pushed. Over 95% of these patients were recognized to have shock before hypotension was recorded [17]. Unnecessary treatments are in wide use. Steroids are still prescribed for patients with dengue diseases, as are other unproven expensive and high-risk interventions, such as platelet concentrates, AC-17 (carbazochrome sodium sulfonate), and aggregated gamma globulin [18-21].

Bleeding

Bleeding is a frequent cause of severe dengue illness, especially in adults. Here, the physician must distinguish between bleeding complicating hypovolemia from unrecognized vascular permeability and that from focal hemorrhaging (for example, in peptic ulcer disease) [4]. Severe but occult bleeding can be difficult to recognize.

These patients exhibit severe hemodynamic instability but with a relatively normal HCT compared with those with only plasma leakage (39.5% versus 45%, $P = 0.032$) [22]. Many patients with severe bleeding have initial or ongoing plasma leakage that keeps the HCT in the normal range despite the severe bleed. Importantly, the administration of blood products such as platelets and fresh frozen plasma to treat patients with threatened blood loss does not hold up to careful scrutiny [22].

Complications

Chronic diseases, particularly in older patients, interact with dengue infections producing a stormy course and, in some cases, a fatal outcome. Deaths have been reported in older patients experiencing primary dengue infections. Risk factors for fatal outcome in adults include diabetes, chronic obstructive pulmonary disease, renal failure, and cardiovascular disease [23,24].

Implications for clinical practice

The requirement for acute and rapid fluid repletion together with possible blood loss makes for a volatile mix, and in the absence of competent emergency and critical care, too many patients have been lost to dengue shock due to hemorrhagic or multi-organ failure complications. In recent decades and certainly since 1988, aggressive efforts by clinical leaders in major Southeast Asian countries have brought about a transformation of treatment protocols for DHF/DSS, with a corresponding drop in case fatality rates [15,17,19,25,26]. A corresponding effort to organize and train physicians in emergency and critical care practices of dengue will be required in the Americas.

Fortunately, many if not most patients with dengue infections experience a rapid onset of high fever and seek treatment early. For those patients presenting within the first two days of onset of fever, new rapid tests that detect dengue viral RNA or a dengue NS1 (nonstructural protein 1) circulating in blood together with a platelet count may make it possible to identify an ongoing acute dengue illness in the clinic [27,28]. Such tests will be available only for a minority of dengue patients. Despite an etiological diagnosis, the physician must still decide which patients have or will soon develop vascular leakage. There is some evidence that gall bladder sonograms may reveal gall bladder wall thickening as an early predictor of dengue vasculopathy [29]. In the absence of this facility, performing a full blood count in the early febrile phase of dengue may be cost-effective. While a drop in total white blood cell count may be the first indicator of a dengue infection, an accompanying early assessment of the HCT provides a reference for comparisons of HCT and detection and fluid management of plasma leakage during the defervescent and critical phases [27].

The majority of dengue cases recover with or without treatment; therefore, the challenge to the clinician is to identify the minority who could progress to severe disease and may die without appropriate interventions after the first few days of fever. In this regard, the critical role that primary health care plays in triage and gatekeeping cannot be overemphasized. As suggested by the World Health Organization Collaborating Center for the Management of DHF in Bangkok, Thailand, clinicians at the front line need to identify the sick patients in need of admission [30]. Adequate oral fluid intake has been shown to reduce the risk of hospitalization for dengue fever and prevent the in-hospital services from being overwhelmed by patients admitted for monitoring for signs of clinical deterioration [31].

It is the authors' experience that primary care facilities in Asia and tropical regions of the Americas are understaffed, under-resourced, and (particularly in the Americas) unprepared to deliver adequate diagnostic or supportive care to dengue patients. It is likely that this results in over-hospitalization. In addition to the need to strengthen diagnostic and treatment abilities of frontline as well as reference center staff, most countries will benefit from organization of a national post-graduate training program similar to the one in Vietnam. Experience has shown that careful triage of out-patients, use of a short-term holding and treatment facility, and an admission strategy that admits only sick patients for the shortest period of time during the critical period provide the best possible prognosis to dengue patients.

Abbreviations

AC-17, carbazochrome sodium sulfonate; DHF, dengue hemorrhagic fever; DSS, dengue shock syndrome; HCT, hematocrit; NS1, nonstructural protein 1.

Competing interests

The authors declare that they have no competing interests.

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