Expediency of dengue illness classification: the Sri Lankan perspective

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DENGUE CLASSIFICATION

South-East Asia is the region with the highest burden of dengue,¹ and has been in the forefront of the development of case classification and management.² Historically, dengue was considered an incapacitating but largely non-fatal illness. During the late 1950s, outbreaks of fatal haemorrhagic fever in children in Thailand and several other South-East Asian countries changed this perception.³⁶ Clinical information gathered during these early outbreaks was the basis for dengue clinical classification published in the 1975 World Health Organization (WHO) guidelines, which were subsequently updated in 1997.⁷⁸ Dengue illness was classified as two distinct clinical entities: dengue fever (DF) and dengue haemorrhagic fever (DHF). In this classification, the main pathophysiological change differentiating DHF from DF in clinically suspected febrile patients is evidence of progressive and selective plasma leakage lasting 24–48 hours (the “critical period”) denoted by haematological, radiological and clinical evidence in that order of appearance. It is important to note that this classification served a dual purpose; surveillance and clinical management.

The guidelines for prevention and control of dengue and DHF published by the WHO South-East Asia Regional Office (SEARO) in 2011 further revised the 1997 classification. In this revised classification, DHF was subdivided into non-shock and shock replacing Grades I and II and Grades III and IV, respectively. In addition, unusual manifestations seen among only a minority of patients with severe organ involvement, such as liver, kidney, brain or heart (isolated organopathy), associated with dengue illness were classified as expanded dengue syndrome or unusual manifestations.⁹

To address concerns, particularly in clinical settings, regarding application of the 1997/2011 WHO classification, the WHO Special Programme for Research and Training in Tropical Diseases (WHO TDR) classification was proposed in 2009¹⁰ and apparently further updated in 2012.¹¹ This classification defines three different levels of clinical dengue illness: Dengue, Dengue with Warning Signs and Severe Dengue. A study done in Sri Lanka in 2011,¹² which used the 2009 WHO TDR classification because it was more user friendly, found that the majority of DF patients had warning signs. This finding indicates that the warning signs are rather nonspecific. According to the WHO TDR classification, patients with warning signs require strict observation; since these patients form the majority, compliance with the WHO TDR guidance would probably overburden clinical facilities. Furthermore, in the 2009/12 WHO TDR classification “clinical” accumulation of fluid is categorized as a warning sign. However, this physical sign typically presents late and, by the time it is clinically detectable, the patient may already have progressed to impending shock. This predicament has possibly created confusion among clinical practitioners in many countries including Sri Lanka. Therefore, we note that the 2009/12 WHO TDR classification has not given clinicians the anticipated ease of application for successful case management.

Two perspective articles were published recently, entitled “Dogma in classifying dengue disease”,¹³ and “Dengue: syndromic basis to pathogenesis research, inutility of the 2009 WHO case definition”.¹⁴ The authors argued over a number of important issues pertaining to dengue illness classification faced today. From a clinical standpoint it is essential to make all efforts to reduce substantially the morbidity, complications and mortality – whatever the classification used. An informal expert consultation on case management of dengue was held in August 2013 in Colombo, Sri Lanka organized by the WHO SEARO with the participation of country representatives and experts from the region. The overall objective of the meeting was to appraise the current status of the use of case classifications in the region. Here, we briefly describe the best use of these classifications and their challenges in application in the Sri Lankan perspective.
the first serologically confirmed in Sri Lanka in 1962, with the first outbreak reported in 1965. Thereafter, multiple outbreaks of DF were reported with only occasional reporting of DHF, a potentially life-threatening condition. DHF was first reported as a public health problem in Sri Lanka in 1989. Since early 2000, progressively larger epidemics of dengue with more cases of DHF have occurred at regular intervals. A major upward shift to a high incidence of dengue has been reported since 2009, with a markedly high DHF proportion of 10–15%.

Classification of dengue illness is important for surveillance and clinical diagnosis and management. The main objective of surveillance is to have a sensitive tool to identify possible dengue cases early for public health intervention. In Sri Lanka, an integrated surveillance system of communicable diseases includes dengue and has island-wide coverage through trained and dedicated clinical and public health staff. National surveillance data are based on timely, high-yield reports that capture symptomatic dengue patients classified by use of the 1997/2011 system. The highest-ever total of 44,461 dengue cases (220 cases/100,000 population) was notified in 2012, approximately a quarter of whom were children younger than 15 years.

Over the past several years a number of activities were initiated in Sri Lanka to strengthen and standardize early detection and management of DHF. The key activities were: development and dissemination of national guidelines; training of all levels of clinical staff based on these guidelines; institutionalization of mandatory patient monitoring charts; capacity building by establishing high-dependency units in major hospitals; and regular clinical and death audits. Furthermore, two centres of excellence were recently established to allow closer observation of children and adults undergoing treatment; hands-on training for clinical staff; and research.

In Sri Lanka, DHF is reported among all age groups from most parts of the country. DHF cases are more common in urban areas with hyperendemic transmission and tend to be younger than DF patients (Epidemiology Unit, unpublished data). We encounter two conflicting clinical practice scenarios. Most practising clinicians actively look for plasma leak among “potential leakers” (patients with fever beyond two days with a platelet count dropping towards and below 100,000 mm³) and provide fluid therapy judiciously, based on the haemodynamic status of each patient. A minority of clinicians largely depend on warning signs as predictors of severe disease, diagnose severity according to clinical end-points and manage cases accordingly. Most clinicians have realized the importance of detecting plasma leak that is preceded by a drop in platelet count around the time of defervescence. This observation has helped in early differentiation of DHF, thereby minimizing disease severity and the occurrence of complications needing adjunctive therapy. Notably, in a minority of patients with no comorbidities, coinfections or unusual manifestations such as massive bleeding (without leaking), the case-fatality rate remains proportionately higher. This high fatality probably reflects late detection of plasma leakage and therefore delayed initiation of appropriate fluid therapy. This observation supports what Scott Halstead has referred to as clinicians having varying degrees of experience, training and clinical skills that probably influence the disease outcome. We believe Sri Lanka has invested wisely to reach the lowest-ever case-fatality rates of 0.28% in 2013 (from 5% in 1996) against a background of a very high dengue incidence. In our opinion, lowering mortality is a clinician’s top priority and has been handled effectively in Sri Lanka in recent years. Despite this success, some clinicians continue to struggle to classify dengue illness effectively for case management.

The 1997/2011 WHO classification identifies DF and DHF as two distinct entities; by contrast, the 2009/12 WHO TDR classification considers that “dengue is one disease entity with different clinical presentations and often with unpredictable clinical evolution and outcome”.

In all parts of Sri Lanka, dengue illness is now considered as a differential diagnosis in patients presenting with acute onset of fever with or without classical features of dengue. When there is a mandatory complete blood count done on day 3 of illness onwards, the appearance of leukopenia and subsequent thrombocytopenia aids the diagnosis. Among other criteria, warning signs of severe illness are considered when admitting patients to hospital from day 3 onwards. The relation between the drop in platelet count towards and below 100,000 mm³ with concurrent and consistent haemoconcentration evidenced by a rapid rise in haematocrit towards 20% from the baseline appears to be unique to DHF and helps to distinguish DHF from DF and other acute febrile illnesses. This is the major advantage of the 1997/2011 WHO classification, which has helped to guide clinicians to manage patients without allowing complications of severe dengue to arise, making DHF a “predictably treatable illness”. Furthermore, it is noteworthy that a substantial proportion of patients who develop potentially severe features do not show any of the warning signs described in 2009/12 WHO TDR classification during the febrile phase.

Heavy reliance on warning signs in anticipation of worsening clinical status without a proper monitoring regime has repeatedly been found to result in unwarranted consequences. As rightfully mentioned by Halstead, not all patients as well as treatment centres do equally well. Having reviewed the 1237 dengue-related deaths reported over the past decade in Sri Lanka, we are yet to find many cases where the primary cause of death was not related to prolonged and repeated shocks as a consequence of delayed and inappropriate treatment or fluid overload due to over treatment with intravenous fluids without proper monitoring (Epidemiology Unit, unpublished reports). We have observed that the 2009/12 WHO TDR classification provides severity-based end-points (whether natural oriatrogenic) and enables better classification of clinically severe cases. The progressive nature of plasma leak in DHF warrants close clinical and laboratory evaluations and proactive action. Therefore, we reiterate that the main challenge for clinicians is timely decision-making to guide management to handle the fluctuating spectrum of clinical syndrome using the classifications appropriately.
The intention of this Perspective was not to do an exhaustive comparison of the two classifications. No doubt, in terms of surveillance as well as diagnosis and management both classifications have their own advantages and disadvantages. Both classifications were born and do exist under the auspices of the WHO. However, countries with limited logistics and human resources struggle to identify what is best for their own use. It is now time to create a formal platform for both groups to sit around one table together with representatives from countries and develop a common guideline classifying dengue illness best applicable to all. Validation of these classifications as a tool for clinical management should be focused to study the impact of their use in changing the course of the disease and its related outcome.

REFERENCES


