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Perspective Piece

Dengue: The Syndromic Basis to Pathogenesis Research. Inutility of the 2009 WHO Case Definition

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Dengue diseases comprise major health problems for around half of the world's population[1]; each year millions of patients with overt dengue infections are seen by thousands of clinicians with varying degrees of experience, training, and clinical skills. The clinical records they generate feed into an ever-expanding dengue research community and contribute to burgeoning scientific literature. Laboratory researchers are dependent upon careful clinical observations that, in turn, are given a clinical diagnosis. For the patient with a dengue infection in most cases this means selecting a diagnostic term based upon case definitions promulgated by the World Health Organization (WHO). In 2009, WHO issued new case definitions that combine disparate clinical responses into diagnostic categories that when widely adopted almost certainly will adversely affect the analytic clarity needed to understand mechanisms underlying dengue pathophysiology, pathogenesis, treatment, and therapeutics. How this might occur is the subject of this perspective.

In 1975, in response to the urgent need to reduce case fatality rates the Southeast Asian and Western Pacific regions of WHO convened meetings that issued Technical Guides that standardized treatment, as well as clinical and laboratory diagnostics, and issued clinical case definitions (Table 1). These were designed to alert physicians to the physiological markers of life-threatening dengue hemorrhagic fever (DHF) or the dengue shock syndrome (DSS).[3] These WHO Guidelines were updated in 1986 and 1997.[2,4] As dengue case attack rates increased and disease became widespread in Asia and the Americas many clinicians and epidemiologists, confronting the full spectrum of dengue illnesses for the first time, encountered difficulties in applying the 1997 case definitions to triage, treatment, or reporting of cases.[5–11] For this reason and because during the past three decades DHF/DSS case definitions had become separately tailored to meet regional or national needs a global WHO survey found that national guidelines for diagnosis and management of dengue cases diverged widely.[12] These problems led to a multicenter study involving 1,585 patients with confirmed dengue infections admitted to 11 hospitals in four Asian and three American countries.[13] The experience gained from this multicenter study led a group of clinicians, basic scientists, and epidemiologists under WHO sponsorship to prepare new case definitions (Table 2) and a new case management algorithm.[14]

The 2009 WHO Guidelines define three different levels of clinical response to dengue infection: Dengue, Dengue with Warning Signs, and Severe Dengue. The criteria for Severe Dengue are presented in slightly differing short and long forms (Table 2). Because the short form is widely displayed on posters this will be a focus of comment. Severe Dengue includes plasma leakage and dengue shock syndrome, which are less quantitatively defined than DHF and DSS in the 1997 WHO Guidelines. Severe dengue also includes several other clinical entities and endpoint diseases, some linked to the fundamental biology of dengue infections, others of iatrogenic origin, and others of as yet unknown pathogenesis.

The new case definitions appear to satisfy some in the health care system. Based upon interviews of 1,288 health workers and reviews of 1,869 charts of patients with confirmed dengue in 18 countries in Asia and the Americas, the acceptability and user friendliness of the new case definitions were judged superior to those of the 1997 version.[15] The new case definitions have received favorable reviews in hospital-based studies in Nicaragua and Indonesia.[16,17] However, because the 2009 WHO guide recommended that cases of Dengue with Warning Signs and Severe Dengue be admitted to a hospital, experienced clinicians in Thailand have expressed concern that this practice could result in over-admission of patients to hospitals during epidemics, possibly reducing the efficiency of patient triage and adversely affecting the quality of clinical case management.[18,19]

Here, we discuss the impact that the widespread adoption of the 2009 WHO case definitions may have on the development of research hypotheses or the conduct of research on dengue diseases.

It may be useful to review the process by which the 1997 WHO case definitions evolved. Children hospitalized in Thailand in the 1950s and early 1960s, many with severe gastrointestinal hemorrhages, were labeled "Thai hemorrhagic fever" (THF).[20] This disease appeared to be of mixed etiology as dengue and chikungunya viruses were isolated and a bewildering mix of primary and secondary serological responses was observed. A specially designed clinical research ward succeeded in identifying dengue shock, a syndrome consisting of abnormal hemostasis, thrombocytopenia, positive tourniquet test, hemorrhagic signs, vascular permeability and shock occurring abruptly about the time of defervescence.[21–23] This syndrome was and still is recognized as unique among acute human infectious diseases.[21,24] When laboratory data were analyzed based on DSS the "two infection" hypothesis of dengue pathogenesis emerged and with it the terms DHF (non-shock) and DSS. Case definitions prepared were designed to focus physician attention to the identification of abnormal hemostasis and clinically significant fluid loss; the term "hemorrhagic" was retained because overt hemorrhages were observed in many cases.

Much of the framework for understanding the etiology of dengue disease, the phenomenon of antibody-dependent

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TABLE 1

1997 World Health Organization (WHO) case definition for dengue hemorrhagic fever and dengue shock syndrome*

DHF, the following must all be present:
Fever, or history of acute fever, lasting 2–7 days, occasionally biphasic
Hemorrhagic tendencies, evidenced by at least one of the following:
A positive tourniquet test
Petechiae, ecchymoses, or purpura
Bleeding from the mucosa, gastrointestinal tract, injection sites, or other locations
Hematemesis or melaena
Thrombocytopenia (100,000 cells/mm^3 or less)
Evidence of plasma leakage caused by increased vascular permeability, manifested by at least one of the following:
A rise in the hematocrit equal to or > 20% above average for age, sex, and population
A drop in the hematocrit following volume replacement treatment equal to or > 20% of baseline
Signs of plasma leakage such as pleural effusion, ascites, and hypoproteinemia
Case definition for dengue shock syndrome:
All of the above four criteria for DHF must be present, plus evidence of circulatory failure manifested by:
Rapid and weak pulse, and
Narrow pulse pressure (< 20 mm Hg)
or manifested by:
Hypotension for age, and
Cold, clammy skin and restlessness.

*HF = dengue hemorrhagic fever.

TABLE 2

2009 World Health Organization (WHO) dengue case definitions*[14]

Probable dengue
Live in or travel to dengue endemic area, fever and two of the following:
Nausea, vomiting
Rash
Aches and pains
Tourniquet test positive
Leucopenia
Any "Warning Sign"
Dengue with Warning Signs
Abdominal pain or tenderness
Persistent vomiting
Clinical fluid accumulation
Mucosal bleed
Lethargy, restlessness
Liver enlargement > 2 cm
Laboratory increase in HCT concurrent with rapid decrease in platelet count
Severe dengue (short form)
Severe plasma leakage
Shock (DSS)
Fluid accumulation with respiratory distress
Severe bleeding (as evaluated by clinician)
Severe organ involvement
Liver AST or ALT >/= 1,000
CNS impaired consciousness
Heart and other organs
Severe dengue (long form)
There is evidence of plasma leakage, such as:
High or progressively rising hematocrit;
Pleural effusions or ascites;
Circulatory compromise or shock (tachycardia, cold and clammy extremities, capillary refill time greater than 3 seconds, weak or undetectable pulse, narrow pulse pressure or, in late shock, unrecordable blood pressure).
There is significant bleeding
There is an altered level of consciousness (lethargy or restlessness, coma, convulsions).
There is severe gastrointestinal involvement (persistent vomiting, increasing or intense abdominal pain, jaundice).
There is severe organ impairment (acute liver failure, acute renal failure, encephalopathy or encephalitis, or other unusual manifestations, cardiomyopathy) or other unusual manifestations.

*HCT = hematocrit; DSS = dengue shock syndrome; AST = aspartate aminotransferase; ALT = alanine aminotransferase; CNS = central nervous system.

enhancement of infection and concepts of T cell immunopathology, has developed out of studies on the dengue vascular permeability syndrome. As illustrated below, if in the future pathogenesis research is based upon clinical responses included in Severe Dengue such patients will exhibit an admixture of dengue disease syndromes and/or complications of treatment, such as 1) the distinct syndromes contained within the clinical category "severe bleeding," 2) inclusion of clinical endpoints that may confuse natural with iatrogenic evolution of disease.

Severe bleeding. During the global dengue pandemic as dengue virus spread to susceptible populations it was recognized that severe gastrointestinal (g.i.) bleeding from duodenal or gastric ulcers or hemorrhagic gastritis occurred in adults during primary dengue infections. It had already been established that g.i. hemorrhages were seen in children during a second dengue infection as a late consequence of uncorrected vascular permeability shock (whether detected or not).[25,26]

A proportion of dengue patients who bleed from focal g.i. lesions may be in shock and require blood transfusions or emergency surgery. These patients are not hemoconcentrated and do not lose fluid into serosal spaces. In a recent study of 644 Vietnamese adults hospitalized with confirmed dengue infections, 40 experienced severe bleeding without vascular permeability.[27] In 26 patients, bleeding was from mucosal sites, whereas 13 had severe epistaxis. Liver damage may have contributed to the dengue bleeding diathesis as their aspartate aminotransferase and alanine aminotransferase levels were significantly elevated.[27] Menorrhagia and bleeding from other damaged tissues have also been seen in adults with dengue infections.[28–32]

During hypotension blood is shunted from the splanchnic to the cerebral vascular system resulting in tissue anoxia in the g.i. tract. As shown at autopsy, shock-related g.i. bleeding is by diapedesis.[33] Without early proactive and careful fluid resuscitation g.i. bleeding may occur often in shocked patients. Children may be more susceptible to vascular permeability shock-related g.i. bleeding than adults because of age-related differences in the integrity of vascular endothelial barriers.[27,34,35] Because of increased peripheral vascular resistance, patients in dengue shock frequently manifest a narrow pulse pressure with normal systolic values. For this reason dengue shock may not be recognized.

Fluid accumulation with respiratory distress. The onset of vascular permeability during dengue infection can be very rapid, varies in severity and evolution from case to case, and ceases abruptly. Shock may be the outcome if fluid lost from the intravascular compartment is not replaced. Dengue shock does not evolve naturally into respiratory distress. As has been recognized for 50 years, uncontrolled administration of intravenous fluids to patients with dengue vascular permeability may result in hypervolemia, accumulation of fluid in the lungs, and pulmonary edema.[36,37] Without careful observation and management of the administration of crystalloids and/or colloids dengue patients may slip rapidly from shock to pulmonary edema.[38] Respiratory distress, although a

severe and life-threatening component of the reality of the treatment of dengue shock, is not an endpoint of dengue disease but an iatrogenic complication.

It is not known if the mechanism(s) of g.i. hemorrhage in the two immunologically different scenarios described previously are or are not the same. Clinically, it is important to arrive at the correct diagnosis as hemorrhaging evolving under these different circumstances requires completely different critical care interventions. For studies designed to identify viral etiology, physiological and immunological status, human genetic input and epidemiological antecedents, these two types of g.i. bleeding must be differentiated. On the basis of recent literature, it is easy to predict that sophisticated laboratory techniques or analyses will be applied to cases based solely upon WHO case definitions. The g.i. hemorrhage of any cause will be labeled "Severe Dengue" in the 2009 WHO case definitions. Similarly, the inclusion of patients with an iatrogenic complication of treatment of the dengue vascular permeability syndrome labeled as "Severe" may upgrade a case that had exhibited only modest vascular permeability or conceivably, none. Both instances exemplify serious misclassification.

Research on pathogenesis of human diseases requires careful delineation of clinical responses. Many children, particularly the young, experience convulsions with high fever. Is this type of impaired consciousness to be labeled "Severe Dengue?" Is severe bleeding or severe involvement of the brain, liver, or heart always directly related to the dengue vascular permeability syndrome? If not, then perhaps to infecting virus strain, concurrent host pathologies, human genetics, or other factors? Use of the single diagnostic term, "Severe Dengue" may combine a mixture of iatrogenic complications, host pathologies, severe organ impairment with and without clinically significant vascular permeability. Which is which? Perhaps individual syndromes can be teased retrospectively from hospital records?[39] In the past, this has proven difficult. Because the 2009 WHO case definitions do not require laboratory tests for the diagnosis of Severe Dengue, retrospective identification of patients with clinically significant vascular permeability from data on hospital charts may be difficult indeed. Once the new diagnostic system is incorporated into the International Classification of Diseases, separation of different dengue clinical syndromes in clinical records may become impossible. Pathogenesis research should be conducted as much as possible on carefully defined categories of human disease response. This requires splitting, not lumping. The 2009 WHO Case Definitions must be revised to permit identification and study of distinct dengue syndromes.

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