The World Health Organization dengue case classifications

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Dengue, a viral haemorrhagic fever causes a significant burden to healthcare systems of countries in the tropics and subtropics (1,2). In recent years, considerable variations in disease presentations involving different organ systems have been documented (1, 3-7). The clinical importance of the different dengue case classifications has been a matter of debate (8,9). The 1997 World Health Organization (WHO) dengue classification, classified the disease as: dengue fever (DF), dengue haemorrhagic fever (DHF), and dengue shock syndrome (DSS). In 2009, a revised classification was released which classified the disease into “dengue” and “severe dengue”, with or without “warning signs” (Table 1) (8,10).

Retrospective studies from Brazil and South-East Asia have compared the two WHO dengue case classification systems (Table 2 (11-16)). In 2011, Barniol, *et al.*, included patients from the Eastern Mediterranean, American and South-East Asian regions and concluded the 2009 classification had greater clinical usefulness in dengue case management and surveillance (16). A large retrospective Brazilian study found considerable agreement between the two classification systems, but the 2009 guidelines had a higher sensitivity in the diagnoses of severe cases (11). Similar studies from Southeast Asia also found the 2009 classification to be more useful clinically (14,15).

Studies from Sri Lanka have also compared the two dengue classification systems (Table 1). In 2017, Sri Lanka faced its largest dengue epidemic (17, 18). A large multicentre study (that included more than

1500 patients) from Sri Lanka during this epidemic compared the two WHO dengue classification systems (9). The 2009 dengue classification was found to be better at detecting disease severity. The number of warning signs correlated with the severity of dengue and the presence of four or more warnings signs was found to be significantly associated with severe dengue. A major drawback of the 1997 dengue classification is that it focuses mainly on plasma leakage and its associated haemodynamic instability, and fails to consider organ dysfunction as a manifestation of disease severity. For example, in the Jayarajah, *et al.*, study, three DF patients were reclassified as severe dengue (according to the 2009 classification) due to the presence of organ dysfunction and excessive bleeding (9). Wanigasuriya, *et al.*, and Bodinayake, *et al.*, also found the 2009 dengue classification to be more useful (19, 20). Similarly, Jayaratne, *et al.*, found the 2009 classification to be better and clinical findings such as abdominal pain, vomiting and bleeding manifestations were more prevalent in severe dengue (21).

Although the 2009 WHO dengue classification was more useful in diagnosing clinically severe disease, there are several practical concerns. According to the 2009 guidelines, only one warning sign is sufficient to alert physicians to the need for immediate assessment or intervention. Although, waiting for more than 3 warning signs to manifest would increase the predictive value, it may considerably delay diagnosis and intervention, and the patient may develop more severe disease with complications (9).

Table 1: WHO dengue case classifications

WHO 1997 dengue classification	WHO 2009 dengue classification	WHO classification of Dengue infections and grading of severity 2011			
Dengue Fever (DF) Acute febrile illness with two or more of the following: ☐ Headache ☐ Retro-orbital pain ☐ Myalgia ☐ Leukopenia ☐ Arthralgia ☐ Rash ☐ Hemorrhagic manifestations ☐ Supportive serology or occurrence at the same location as other confirmed cases of dengue fever	Dengue without warning signs Fever and two of the following: ☐ Nausea, vomiting ☐ Rash ☐ Aches and pains ☐ Leukopenia ☐ Positive tourniquet test Dengue with warning signs Dengue as defined above with any of the following: ☐ Abdominal pain or tenderness ☐ Persistent vomiting ☐ Clinical fluid accumulation ☐ Mucosal bleeding ☐ Lethargy, restlessness ☐ Liver enlargement > 2 cm ☐ Laboratory: increase in HCT concurrent with rapid decrease in platelet count	DF/DFH	GRADE	SIGNS and symptoms	Laboratory
		DF		Fever with two of the following: Headache. Retro-orbital pain. Myalgia. Arthralgia / bone pain. Rash. Haemorrhagic manifestations. No evidence of plasma leakage.	Leucopenia (wbc 5,000 cells/mm ³) Thrombocytopenia (Platelet count <150,000 cells/mm ³) Rising haematocrit (5% - 10%) No evidence of plasma loss.
		DHF: non-shock	DHF-I	Fever and haemorrhagic manifestation (positive tourniquet test) and evidence of plasma leakage	Thrombocytopenia <100,000 cells/mm ³ HCT rise 20%
Dengue Hemorrhagic Fever (DHF) All of the following must be present: Fever or history of acute fever, lasting 1-7 days, occasionally biphasic Hemorrhagic manifestations: - Positive tourniquet test; - Petechia, equimosis, purpura or bleeding from mucosa, gastrointestinal tract, injection sites or other locations; or - Haematemesis/melena Thrombocytopenia (<100,000 platelets per mm ³) Evidence of plasma leakage due to increased vascular permeability	Severe dengue Dengue with at least one of the following criteria: Severe plasma leakage leading to: - 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 - failure of heart and other organ	DHF: shock	DHF-II	As in Grade I plus spontaneous bleeding.	Thrombocytopenia <100,000 cells/mm ³ HCT rise 20%.
			DHF-III	As in Grade I or II plus circulatory failure (weak pulse, narrow pulse pressure (20 mmHg), hypotension, restlessness).	Thrombocytopenia <100,000 cells/mm ³ HCT rise 20%.
			DHF-IV	As in Grade III plus profound shock with undetectable BP and pulse	Thrombocytopenia < 100,000 cells/mm ³ HCT rise 20%.
Dengue Shock Syndrome (DSS) DHF with hypotension for age or narrow pulse pressure (<20 mmHg), plus one of the following: ☐ Rapid and weak pulse ☐ Cold, clammy skin, restlessness		Expanded dengue syndrome		Evidence of isolated organopathy (unusual manifestations)	

Table 2: Summary of studies comparing WHO 1997 and 2009 dengue case classifications

Author, Year and Country	Study design (N)	Results	Conclusion / Recommendations
Bodinayake, <i>et al.</i> 2018, Sri Lanka	Prospective (N=976)	The treating physician's clinical diagnosis of dengue at discharge was found to be more sensitive than the 2009 WHO classification. However, diagnosis on admission was less sensitive than the 2009 WHO classification.	The 2009 WHO dengue classification system had high sensitivity but low specificity vs. clinical diagnosis at presentation.
de Silva, <i>et al.</i> 2018, Brazil.	Retrospective (N=30,670)	The 2009 WHO classification was found to be more sensitive in identifying severe dengue cases than 1997 WHO classification. Most severe cases detected by 2009 WHO classification may be an overestimate, as of the 27.4% of patients who were classified as DWS, 90.4% did not develop hypotensive shock.	Patients with severe disease were detected more using the 2009 WHO classification. However, clinicians should chose the guideline by considering the applicability at ward setting.
Jayarajah, <i>et al.</i> 2017, Sri Lanka	Prospective (N=1878)	The correlation between the two dengue case classification systems was not satisfactory. Three patients with DF were reclassified as severe dengue using the 2009 WHO classification. Number of warning signs correlated with sever disease. The 2009 WHO classification was better for identifying patients who may develop severe disease.	The 2009 WHO classification was more useful than the 1997 WHO classification in predicting patients who were likely to develop severe disease.
Zakaria, <i>et al.</i> 2014, Malaysia	Retrospective (N=281)	Majority of patients who were categorized as DF using the 1997 WHO classification were categorized as DWS in the 2009 WHO classifications.	The revised WHO 2009 guidelines classified more patients into a category that needs a higher level of care.
Jayaratne, <i>et al.</i> 2012, Sri Lanka.	Prospective (N=184)	The presence of the warning signs were higher in patients with severe dengue. Presence of 5 or more warning signs as well as several laboratory investigations were associated with the development of severe dengue.	The 2009 WHO warning signs were useful in predicting patients who may develop severe dengue.

Author, Year and Country	Study design (N)	Results	Conclusion / Recommendations
Tsai, <i>et al.</i> , 2012, Taiwan	Retrospective (N=148)	2009 WHO classification was able to differentiate varying levels of clinical severity of DF better than the 1997 WHO classification.	The 2009 WHO classification was found to be more effective in identifying patients who may develop severe cases of dengue.
Barniol, <i>et al.</i> , 2011 18 Countries	Prospective (N=1156) and retrospective (N=2092)	The revised 2009 WHO classification system was shown to be more sensitive for early recognition of severe disease than the 1997 WHO classification.	The revised 2009 WHO dengue classification had better potential for case management and surveillance than the 1997 WHO classification.
Wanigasuriya, <i>et al.</i> , 2011, Sri Lanka	Prospective (N=106)	The revised 2009 WHO classification was more sensitive to cases that may progress to severe dengue than the 1997 WHO classification.	Revised 2009 WHO classification was more applicable and practical in the ward setting.
Basuki, <i>et al.</i> , 2010, Indonesia	Prospective (N=122)	Some cases with severe disease did not fit into the 1997 WHO classification	The revised 2009 WHO dengue classification system was better at detecting severe dengue infections than the 1997 WHO classification system
Lima, <i>et al.</i> , 2010, Brazil	Retrospective (N=187)	When the two classifications were compared, the majority of the DF patients (70%) were reclassified as DWS or severe dengue by 2009 WHO classification.	The 2009 WHO classification was more effective in identifying patients who developed severe cases of dengue.

DF: Dengue fever, DHF: Dengue haemorrhagic fever, WHO: World Health Organization, DWS: Dengue with warning signs

DSS can be difficult to diagnose by inexperienced health care professionals, as patients may remain remarkably well in the early stages of shock and then deteriorate rapidly. In the 2009 WHO dengue classification, some criteria are not well-defined and may lead to differences in clinical assessment among physicians. For example, criteria such as: presence of severe bleeding and severe organ dysfunction are expected to be clinically judged by the treating physician. Thus, the diagnosis of severe dengue may vary among clinicians. This limitation should be overcome by more specific criteria for assessment of bleeding and organ dysfunction (9). Furthermore, in the 2009 classification “clinical” accumulation of fluid” is recognised as a warning sign. Clinical fluid accumulation occurs late and when fluid leak becomes clinically detectable, progression to impending shock may have already occurred. Therefore, it is not a useful warning sign in the clinical setting (22).

Furthermore, the 2009 classification may be difficult to practically incorporate into clinical practice in resource limited settings of developing nations due to the lack of rapid diagnostic tests and as most warning signs are not specific to dengue and may be seen in other tropical infections in such settings (9). In dengue endemic countries like Sri Lanka, all patients who present with fever and warning signs will invariably be diagnosed as having dengue with warning signs and warrant hospital admission for observation. This may increase in-hospital case-loads and in-turn put pressure on limited health budgets (9). Therefore, the 2009 classification needs revision to overcome these limitations and to be more clinically relevant.

Plasma leakage leading to haemodynamic instability with organ failure is a central pathophysiological feature of dengue. This needs to be detected early and promptly managed with fluid therapy to prevent complications. Massive bleeding and shock is more common in adults than children due to intake of NSAIDs, underlying peptic ulcers or due to late presentation (9). Furthermore, comorbidities such as diabetes mellitus, hypertension, ischaemic heart disease, chronic liver or kidney disease are more prevalent among adults and may complicate the clinical picture. Thus, in the WHO SEARO 2011

massive bleeding, co-morbidity and co-infections were added as Expanded Dengue Syndrome (EDS) (Table 1) (9).

In conclusion, from studies done so far, the 2009 WHO dengue classification appears to be clinically more useful in detecting severe disease. However, the 2009 WHO dengue classification is still not the ideal classification for clinical use especially in resource limited developing countries. We have highlighted several limitations that should be addressed to make it more clinically relevant. Furthermore, any future dengue case classifications should cater to developing countries with limited health resources.

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