

WHO 2009 GUIDELINES AND CASE CLASSIFICATION: AN UPDATE AND SHORT REPORT

Olaf Horstick and Silvia Runge-Ranzinger

Teaching Unit of the Institute of Public Health, University of Heidelberg, Germany

INTRODUCTION

In 2009, the World Health Organization (WHO) issued new dengue guidelines (WHO/TDR, 2009), in collaboration with the Special Program for Research and Training in Tropical Diseases (WHO/TDR), for WHO regional offices and many dengue researchers and program planners. One of the key

recommendations was the introduction of the 2009 WHO dengue case classification. This classification describes dengue as 'dengue and severe dengue (D/SD).' Warning signs (WS) have been developed for triage, helping medical staff with symptomatic dengue cases to facilitate the decision of closer surveillance and/or hospitalization (dengue with warning signs (D+WS)) (Fig 1).

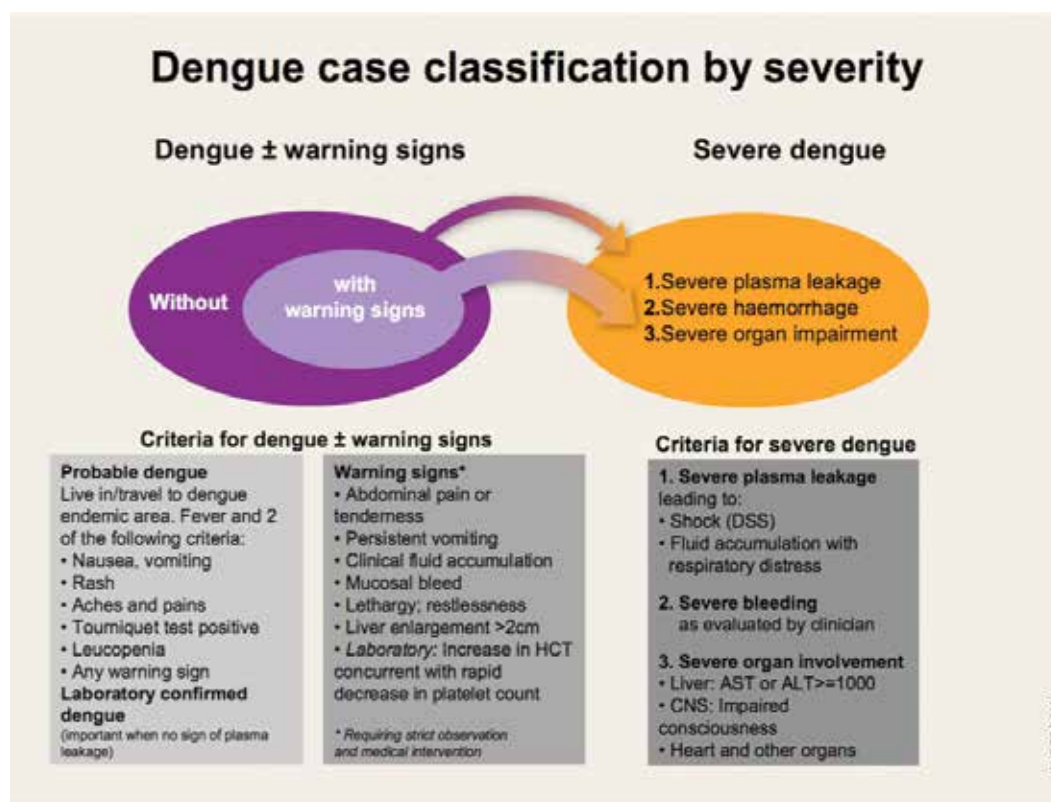


Fig 1– 2009 WHO dengue case classifications.

Correspondence: Olaf Horstick, Teaching Unit of the Institute of Public Health, University of Heidelberg, Germany

E-mail: Olaf.Horstick@uni-heidelberg.de

The 2009 WHO dengue case classification has been developed with a series of studies, in step-by-step procedures, including quantitative and qualitative data, to produce: 1) the largest ever collection of dengue patient data prospectively and globally (Alexander *et al*, 2011); 2) systematic reviews to describe the problems with the previous classification (Bandyopadhyay *et al*, 2006), and studies comparing both classifications (Horstick, 2014a); 3) mixed methods to describe necessities for the 2009 WHO dengue case classification (Santamaria *et al*, 2009) and comparing both classifications (Barniol *et al*, 2011); 4) qualitative methods with experts comparing both classifications (Horstick *et al*, 2015a); and 5) descriptions of the process (Horstick *et al*, 2012, 2015b), detailing the step-by-step procedure.

Furthermore, clinical algorithms have been developed, based on the 2009 WHO case classification (Fig 2) and a clinical handbook (WHO/TDR, 2012).

The question now arises, is the 2009 WHO dengue case classification implemented? There has been controversy about the 2009 WHO dengue case classification, between different research groups (Halstead, 2012; Farrar *et al*,

2013). Advocates for the 1997 WHO dengue case classification continue to use the model dengue fever (DF), dengue hemorrhagic fever (DHF) and dengue shock syndrome (DSS), developed in 1975 by expert consensus, based on studies on Thai children in the 1950's and ~60's, with modifications in 1986 and 1997 (Bandyopadhyay *et al*, 2006). Key differences between the two classifications are summarized in Table 1.

This review aims to update on the implementation process. As a simple review, no formal methods have been used, but including a description of the definitions used by key organizations involved in dengue control (WHO, WHO regional offices, ECDC, CDC, NIH, and including research and clinical support material, as the BMJ) and recommendations including for research.

DISCUSSION

Descriptions of the definitions are used by key organizations involved in dengue control. The International Classification of Diseases 11 update (ICD 11) in its currently available beta-draft uses the 2009 WHO dengue case classification, coding dengue as 1D60 Dengue without warning signs, 1D61 Dengue with warning signs, 1D62 Severe

Table 1. Summary of differences between the 2009 WHO dengue case classification (DCC) and the previous case classification.

WHO DCC	2009 WHO DCC	1997 WHO DCC
Development	Series of studies, both quantitative and qualitative	Expert consensus, based on previous studies and clinical experience
Validation	Tested in many different countries	No formal validation process
Focus	Towards severity of disease and early detection of severe cases	No relation to severity (especially DHF)
Usefulness	Especially for clinical management, but also for improved surveillance	Developed for both clinical management and research
Strength	Inclusion of all severe clinical pictures of dengue Helpful for clinical management without laboratory facilities	Medical staff is trained to use this model
ICD	ICD 11	Previous ICDs
Outlook	Further studies soon available on warning signs and case definitions	

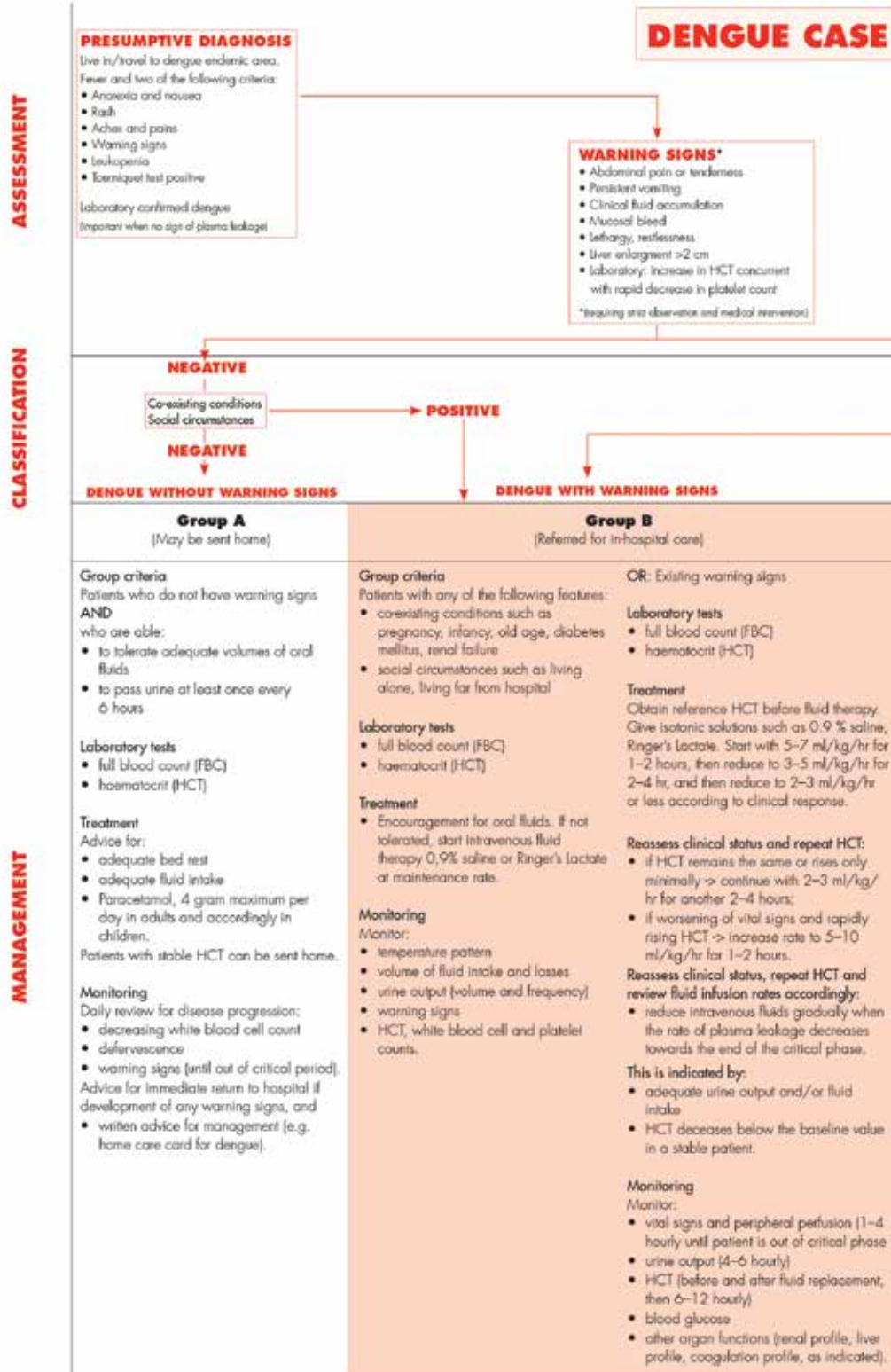
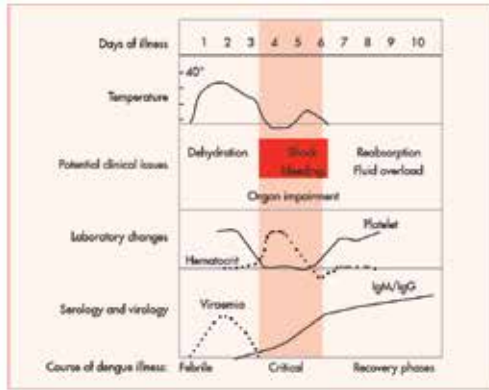


Fig 2– Dengue treatment algorithm, for local adaptation.

MANAGEMENT



POSITIVE

SEVERE DENGUE

Group C

(Require emergency treatment)

Group criteria

Patients with any of the following features:

- severe plasma leakage with shock and/or fluid accumulation with respiratory distress
- severe bleeding
- severe organ impairment

Laboratory tests

- full blood count (FBC)
- haematocrit (HCT)
- other organ function tests as indicated

Treatment of compensated shock

Start IV fluid resuscitation with isotonic crystalloid solutions at 5–10 ml/kg/hr over 1 hour. Reassess patients' condition.

If patient improves:

- IV fluids should be reduced gradually to 5–7 ml/kg/hr for 1–2 hours, then to 3–5 ml/kg/hr for 2–4 hours, then to 2–3 ml/kg/hr for 2–4 hours and then reduced further depending on haemodynamic status;
- IV fluids can be maintained for up to 24–48 hours.

If patient is still unstable:

- check HCT after first bolus;
- if HCT increases/still high (>50%), repeat a second bolus of crystalloid solution at 10–20 ml/kg/hr for 1 hour;
- if there is improvement after second bolus, reduce rate to 7–10 ml/kg/hr for 1–2 hours and continue to reduce as above;
- if HCT decreases, this indicates bleeding and need to cross-match and transfuse blood as soon as possible.

Treatment of hypotensive shock

Initiate IV fluid resuscitation with crystalloid or colloid solution at 20 ml/kg as a bolus for 15 minutes.

If patient improves:

- give a crystalloid/colloid solution of 10 ml/kg/hr for 1 hour, then reduce gradually as above.

If patient is still unstable:

- review the HCT taken before the first bolus;
- if HCT was low (<40% in children and adult females, <45% in adult males) this indicates bleeding, the need to cross-match and transfuse (see above);
- if HCT was high compared to baseline value, change to IV colloids at 10–20 ml/kg as a second bolus over 30 minutes to 1 hour; reassess after second bolus;
- if patient is improving reduce the rate to 7–10 ml/kg/hr for 1–2 hours, then back to IV crystalloids and reduce rates as above;
- if patient's condition is still unstable, repeat HCT after second bolus;
- if HCT decreases, this indicates bleeding (see above);
- if HCT increases/remains high (>50%), continue colloid infusion at 10–20 ml/kg as a third bolus over 1 hour, then reduce to 7–10 ml/kg/h 1–2 hours, then change back to crystalloid solution and reduce rate as above.

Treatment of haemorrhagic complications

Give 5–10 ml/kg of fresh packed red cells or 10–20 ml/kg of fresh whole blood

Dengue and 1DGZ Dengue fever unspecified; furthermore as XB01.81 Dengue virus, QA23.6 Special screening examination for viral diseases other than human immunodeficiency virus, screening for dengue fever, 8D70.2Y Other specified viral encephalitis, encephalitis due to dengue fever and 8D72.2 Viral Myelitis, myelitis due to dengue virus.

With the update, the 2009 WHO dengue case classification should enter into all surveillance systems, which will facilitate reporting for dengue, but also to improve estimates for dengue disease burden, including severity of dengue and costs. This could help in the health policy context as well, underlining the importance to include dengue control in health programs in all affected countries (Horstick, 2014b).

The inclusion of the 2009 WHO dengue case classification in the ICD is closely mirrored by the bigger health organizations globally, WHO reporting for example on dengue fact sheets as “dengue and severe dengue” (WHO, 2016). For the WHO regional offices, the office for Africa, AFRO, follows the WHO dengue fact sheet, but quotes “dengue haemorrhagic fever” on its website (WHO/AFRO, 2017). The Pan American Health Organization, with the regional office for WHO in the Americas (AMRO), uses consistently the 2009 WHO dengue case classification (PAHO, 2017). In the South East Asian Region for WHO however, a separate guideline has been issued in 2011, using DF/DHF/DSS (WHO/SEARO, 2011). For the Western Pacific Regional Office, the 2009 WHO dengue case classification is used, including newly developed training material to explain the differences to the previous classification (WHO/WPRO, 2017).

As for the surveillance centers, the Centers for Diseases Control (CDC) explain in detail the 2009 WHO dengue case classification (CDC, 2015),

...in 1997 the dengue case definition was limited in terms of its complexity and applicability. This recognition of the limitations led to a multicenter study in seven countries in Asia and Latin America and a new case

definition emerged from this study. The new WHO classification for dengue severity is divided into Dengue without Warning Signs, Dengue with Warning Signs, and Severe Dengue.

The European Centre for Disease Control (ECDC), on its websites, uses the terminology of the 2009 WHO dengue case classification, however explaining also, *Severe dengue — commonly referred to as ‘Dengue haemorrhagic fever/Dengue shock syndrome (DHF/DSS)’ to distinguish it from ‘classic’ dengue fever (DF)* (ECDC, nd).

As a support system for research and clinicians, the British Medical Journal shows in their Best Practice Guideline series the use of the 2009 WHO dengue case classification (BMJ, 2016), quoting:

The 1997 dengue case definition... is limited in terms of its complexity and applicability. This led to a new WHO classification where dengue severity is divided into dengue without warning signs, dengue with warning signs, and severe dengue. While WHO still support both case definitions, there is a move towards using the 2009 case definition due to its ease of use”.

One of the areas that were criticized of the 2009 WHO dengue case classification is that research endpoints are not well enough defined, since research may require further clinical endpoints, as also witnessed during the trials of the first available — and partially effective — vaccine (Hadinegoro, 2015), these endpoint measures are now being defined in an empirical process (NIH, 2015). Furthermore, and referring to this argument, the 2009 WHO dengue case classification has been particularly developed to help clinical management, in the crucial area to reduce case fatalities.

In an expert consensus in Havana, Cuba in 2014 (Horstick, 2015a), dengue experts agreed on this argument and described, 1) the need to update ICD10, 2) include D/SD in country epidemiological reports and 3) implement studies improving sensitivity/specificity of the dengue case definition. Most importantly, the group of experts favored

largely the 2009 WHO dengue case classification, with the clinical management implications, since it 1) standardizes clinical management, 2) raises awareness about unnecessary interventions, 3) matches patient categories with specific treatment instructions and 4) makes the key messages of patient management understandable for all health care staff.

In conclusion, with the inclusion of the 2009 WHO dengue case classification in the ICD11 and the adaptation of the classification in most regions in the world, and organizations working in this field, a consensus for its global use is overdue, for the few remaining countries not using this classification model. This could be stimulated by WHO. If a process of updating the 2009 WHO dengue case classification is envisaged, it should however be based on data, this could be quantitative and qualitative, however not based on single expert opinion only. Furthermore, research is ongoing to "fine-tune" the warning signs, and results should become available in the next couple of years. The NIH-lead process to define research endpoints is most welcome, particularly since the next vaccines are entering or coming out of clinical phase 3 trials.

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