Title: Definitions for Warning Signs and Signs of Severe Dengue According to The WHO 2009 Classification: Systematic Review of Literature

Short Title: Definition of warning and severe signs in dengue

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Summary

Since warning signs and signs of severe dengue are defined differently between studies, we conducted a systematic review on how researchers defined these signs. We conducted an electronic search in Scopus to identify relevant articles, using key words including dengue, "warning signs", "severe dengue", and “classification”. A total of 491 articles were identified through this search strategy and were subsequently screened by two independent reviewers for definitions of any of the warning or severe signs in the 2009 WHO dengue classification. We included all original articles published in English after 2009, classifying dengue by the 2009 WHO classification or providing the additional definition or criterion of warning signs and severity (beside the information of 2009 WHO). Analysis of the extracted data from 45 articles showed wide variations among definitions and cutoff values used by physicians to classify patients diagnosed with dengue infection. The establishment of clear definitions for warning signs and severity is essential to prevent unnecessary hospitalization and harmonizing the interpretation and comparability of epidemiological studies dedicated to dengue infection.

Keywords: Dengue, warning signs, severe signs, classification.

Introduction

Dengue is the most prevalent mosquito-borne disease affecting people in tropical and sub-tropical regions of the world. 390 million infections with this virus are estimated to occur annually, but only one-fourth are clinically apparent(1), giving rise to around 20,000 deaths in developing countries(2). Historically, dengue case classification was developed in 1975 by expert consensus based on studies on Thai children in the 1950s and 60s, with modifications in 1986 and 1997(3). The WHO 1997 dengue classification faced a lot of criticism, with many clinicians working in endemic areas finding it difficult to apply with increased reports of severe cases not fitting the criteria for dengue hemorrhagic fever (DHF) in many patients. Thus, this classification underwent a revision by the WHO in 2009 based on experts' opinions, reviews, and the large multi-center study (4) conducted in South East Asia and Latin America.

The revised WHO (2009) guidelines [1] classify patients into three groups: dengue without warning signs (WS), dengue with warning signs, and severe dengue. The WHO 2009 classification (Fig. 1) developed warning signs which help health-care professionals in the clinical triage of more serious patients out of a large pool of dengue patients in epidemic settings(4,5). Although the 2009 classification lists these warning signs and the signs for severe disease, the precise parameters to define these signs clinically are lacking in the guidelines. This leads to the heterogenous application of the guidelines by different physicians for diagnosing and treating dengue patients. Understanding what criteria are currently being used to define the WS is required to move forward and develop a standardized definition and further refine the current WHO guidelines. This would further improve clinical management guidelines and harmonize the interpretation of findings from epidemiological studies. We therefore conducted a systematic review assessing how these warning signs were defined in different studies, with the eventual aim of developing more concise definitions for future updates in the WHO guidelines.

Methods

The study followed the recommendations of Preferred Reporting Items for Systematic Review and Meta-analysis (PRISMA) statement(6), which is available in the supporting documents (Appendix A). The protocol of the study was developed in July 2015 and registered in PROSPERO (ID: CRD42015024105).

Search strategy

Since we aimed to investigate only peer reviewed original articles and Scopus covers more peer review journals than Web of Science and Pubmed, we conducted an electronic search in Scopus database to identify relevant articles using the following keywords: “warning signs”, “severe dengue”, and “classification” as shown in the appendix. Search results were limited to English and original articles. Studies published before 2009 were not included.

Selection criteria

The inclusion criteria are: (1) Original articles indexed at Scopus database and published in English from the year 2010. (2) Retrospective, prospective, or cross-sectional studies providing additional definitions or criteria (beside the definitions/criteria provided by the WHO 2009 classification) of any of the warning or severe signs of dengue infection. (3) The severity of dengue infection must be classified according to the WHO 2009 classification.

The exclusion criteria are: (1) Reports with inadequate information. (2) Non-human, animal, or in vitro studies. (3) Articles in languages other than English. (4) Case reports, review articles, thesis, and books.

Data extraction

Search results were imported into Endnote X7 (Thompson Reuter, CA, USA) for deletion of duplicates. Three reviewers independently screened the references using predetermined eligibility criteria. The full texts of included references were then retrieved through the Library of Nagasaki University, and full-text screening was subsequently conducted to identify relevant references. The data-extraction form was developed based on the WHO 2009 classification criteria of dengue. Next, included articles were reviewed and data extraction was performed by three independent reviewers. Any disagreement in screening and extraction steps was discussed between the reviewers to reach a consensus. Consultation from supervisors (NTH, BW, and KH) was acquired when necessary.

Results

(A) Search results and study characteristics

Searching Scopus yielded 490 articles. A total of 448 articles was excluded for the causes mentioned in the study flowchart (Fig. 2). Characteristics of the 45 included studies are described in (**Table 1**).

(B) Definitions of warning signs

1. Persistent vomiting

Six of the included studies provided a definition for 'persistent vomiting' as a warning sign of dengue (Table 2), which were based on three parameters, including: frequency, duration, and impact. One study required the presence of signs of dehydration on physical examination for vomiting to be considered a "warning sign" of dengue(34). Mercado et al (10) also defined persistent vomiting as Grade 3 and above referring to the Common Toxicity Criteria Manual (CTC Version 2.0)(50).

2. Abdominal pain or tenderness

Five out of the 45 studies provided a definition for abdominal pain. None of the studies reported on the exact duration of pain or the numerical score of intensity required to fulfill the definition. Definitions of abdominal pain in the five studies are summarized in Table 2.

3. Lethargy/restlessness

Five studies provided definition of "lethargy" as a warning sign of dengue (Table 2).

3. Clinical fluid accumulation

Clinical fluid accumulation was defined in seventeen studies, all of which describe pleural effusion and ascites as criteria for clinical fluid accumulation (Table 3). However, the authors' definitions varied depending on the method of detection of fluid accumulation (radiography vs. physical examination). Six studies added that fluid accumulation should be documented by radiography (ultrasound for ascites and chest X-ray for pleural effusion), while another two studies stated that fluid accumulation can be diagnosed either clinically or with imaging.

5. Increase in hematocrit

Twenty-two out of 45 studies gave definitions for 'increase in hematocrit' as a warning sign of dengue. Nineteen studies defined it as an increase in hematocrit by more than 20% from the baseline (9,10,12,17–20,23,27,28,33,35,38,39,43–45,47,48). Macedo et al (20) specified that the 20% increase should be from the baseline value during the convalescent phase of the disease. Thai et al(31), however, defined it as an increase in hematocrit by more than 15% from the baseline. Instead of the increase from the baseline, four studies defined "increase in hematocrit" using a cutoff value for hematocrit that is adjusted for gender(19,28,33,49). Moreover, Rodrigues et al (14) defined "increase in hematocrit" using a

non-adjusted cutoff value of hematocrit > 48%, with no discrimination between males and females. The hematocrit cutoff values used to define "increase in hematocrit" are summarized in Table 4.

6. Rapid decrease in platelet count

The definition of rapid decrease in platelets was described nineteen times in twenty studies (Table 5).

7. Liver enlargement

Fourteen out of sixteen studies used the definition outlined in the WHO 2009 Dengue guidelines (3). Romero-Vega (13) et al and Rathakrishnan et al (15) added "painful hepatomegaly" to the definition of liver enlargement.

8. Mucosal bleeding

Mucosal bleeding, as a warning sign of dengue, is described in fifteen studies (Table 6)**.** Its variable definitions are summarized below (Table 6).

(C) Definitions of severe signs

1. Severe plasma leakage

Severe plasma leakage was variably defined in seven of the 45 studies.

2. Shock

Shock was defined in seventeen studies using different combinations of (1) narrow pulse pressure, (2) hypotension, (3) tachycardia, (4) hypoperfusion, (5) plasma leakage, and (6) undetectable pulse or unrecordable pressure as shown in the Table 7. While a systolic blood pressure less than 90 mm Hg was commonly defined as hypotension (9,12,17,23,42,43,47), Macedo et al (20) used a definition that is specified for age: "Decrease in arterial systolic pressure <5th percentile for age [<PAS5], calculated as age [years] ×2+70". Except for Weg et al. (25) and Macedo et al. (20), all other authors (n=14) considered having narrow pulse pressure alone to be sufficient to label the patient as having "shock". Weg et al required the presence of hypotension, tachycardia, and signs of poor capillary perfusion in addition to narrow pulse pressure. Macedo et al (20) did not consider having "narrow pulse pressure" alone to be defining for shock; and that shock is diagnosed in the presence of at least two clinical signs of hypoperfusion (e.g., slow capillary refill, cold skin, rapid and weak pulse) with or without an associated narrow pulse pressure. Authors reported three signs of poor capillary perfusion: slow capillary refill, cold

extremities, and rapid pulse rate. (20,21,24,29,33,39,43)**.** Slow capillary refill was defined in two studies as having a capillary refill time greater than 3 seconds (33,43).

3. Respiratory distress

Respiratory distress due to clinical fluid accumulation is defined with noticeable variation in four studies (Table 8). Several parameters are used by authors to define respiratory distress, including: respiratory rate, PaO2:FiO2 ratio, oxygen saturation level, oxygen therapy requirement, and respiratory acidosis. All the four studies used respiratory rate as a parameter to define "respiratory distress". However, the cut-off values used were lacking in terms of congruency and consistency: ≥ 24 breaths/min, ≥ 30 breaths/min, ≥ 40 breaths/min, ≥ 60 breaths/min.

4. Cardiac involvement

Cardiac involvement as a criterion for "severe dengue" is reported in twelve studies (Table 7). With the majority of them, eight studies, describing it as « myocarditis » (17,18,21,23,24,32,43,46). Two studies used « heart failure » to describe cardiac involvement (40,49), while one study required the presence of both « myocarditis » and « heart failure » confirmed by echocardiography to fulfill the definition (20). Hoffmeister et al (9), however, described the cardiac involvement as « cardiomyopathy ». Except for Lovera et al (21) and Guerrero et al (32), none of the above mentioned studies reported on the diagnostic criteria for heart failure, cardiomyopathy, or myocarditis.

5. Central nervous system involvement

Ten studies reported central nervous system (CNS) involvement as a criterion for "severe dengue" and they used either encephalitis (9,18,20,21,32,43), encephalopathy (5,17,23) or both (43) to describe "CNS involvement " (Table 7). Lovera et al (21) gave a more precise definition: "impaired consciousness in the absence of metabolic abnormalities or other apparent explanation, or in the presence of any of the following: (1) cerebrospinal fluid pleocytosis (corrected white blood cell count >5/L), (2) focal neurologic signs, and (3) convulsions other than simple febrile seizures." Seizures are mentioned in three studies as a feature of CNS involvement (9,21,27).

6. Renal impairment

Renal impairment is defined by six studies as an increased in serum creatinine ≥ 2 times the upper limit of normal (Table 7). The calculated "normal" creatinine level was determined by two authors (23,47) based

on The Modification of Diet in Renal Disease (MDRD) equation for glomerular filtration rate (GFR) of 75 ml/min. Also, renal impairment is defined by five studies as an increase in serum creatinine ≥ 2 times the "baseline" creatinine level. Moreover, two studies used serum creatinine cut-off values, with or without adjustment for gender, to define renal impairment: Hoffmeister et al (9) defined it as serum creatinine > 1.5 mg/dL in females or > 1.8 mg/dL in females while Aung et al (34) defined it as serum creatinine > 1.2 mg/dL for both males and females.

7. Liver involvement

Eighteen of nineteen studies used the definition outlined in the WHO 2009 guidelines (Table 7) . Lovera et al (21) added that the elevation in transaminases should not be attributed to other causes (e.g., hepatitis A, B, C, or ingestions of potentially hepatotoxic drugs). Hoffmeister et al (9), however defined liver involvement differently: "acute liver failure evidenced by jaundice, thromboplastin time < 20% and encephalopathy."

8. Severe bleeding

Variable definitions of severe bleeding were reported in thirteen studies (Table 7).Nine studies considered any bleeding that requires transfusion of blood or blood products to be "severe"; which is consistent with Grade 3 bleeding on the WHO bleeding scale (53). One study (20) required the presence of unstable hemodynamic status for bleeding to be considered "severe", regardless of the hematocrit level or the need for transfusion of blood products. Aung et al (34) considered any bleeding that needs acute management to control active bleeding (e.g., nasal packing, dental splint) to be "severe". WHO bleeding scale of grade 2 and above (53) was used in one study, Gan et al (47), to define severe bleeding.

Discussion

This review highlights the variability in applying the WHO 2009 classifications with regard to the warning signs and signs of severe dengue infection. Before the WHO 2009 classification, dengue was defined as dengue fever (DF), DHF, and dengue shock syndrome (DSS) according to the 1997 classification. This classification system showed numerous limitations, especially in the clinical evaluation of severe patients (11). The revised 2009 classification has a higher sensitivity to detect the severity of the disease (3,11,54,55). Its specificity, however, is much lower (73.0%) compared to the 1997

dengue classification (93.4%) (20). This lower specificity in part could be attributed to the lack of clear defining criteria for warning signs and signs of severity. We found great variation among authors' definitions of these signs. Of the sixteen warning and severe signs discussed in this review, the authors have only agreed upon the definitions of 'liver enlargement' and 'liver involvement', which are both predefined in the WHO 2009 classification. Definitions of the remaining warning and severity signs lacked consensus. This can be partially attributed to the variation in clinical practice and the presence of national guidelines in different regions in the world. A single clinical parameter or laboratory value may have different defining criteria or cutoff values in different demographic and clinical settings and thus cannot be generalized. For example, 'severe bleeding' was considered by many authors as any bleeding that requires transfusion of blood or blood components. The need for blood transfusion, however, is a clinical decision and may vary between adult and pediatric age-groups as well as between males and females. The preexisting level of hemoglobin before bleeding is also one of the deciding factors that influence the decision to transfuse. Given the large varation in bleeing sites and severity, and a lack of specific guidance in the current WHO classification, bleeding as a sign of dengue severity will require further detailed analysis and precise characterization for future classification updates. Since creatinine level is suggested to be associated with factors other than age and gender such as body mass, this may explain why some authors defined renal impairment as both definitions, serum creatinine ≥ 2 times the upper limit of normal and/or serum creatinine $\geq$ baseline creatinine level, trying to not misclassify their patients.

Several prospective observational studies have attempted to validate the current warning signs as predictive markers for the development of severe disease (56). The largest study to date, which has recently completed recruitment is a multi-centre prospective study by IDAMS (International Research Consortium on Dengue Risk Assessment, Management and Surveillance) (57), which has enrolled >8000 dengue patients, is a trial to identify early (<72 hours fever) clinical and laboratory parameters associated with progression to a more severe disease. The results from this study plus others provide a large cohort of patients, which can be used to not only validate the warning signs but also to develop a more robust clinical case definition for dengue and assist in refining the current definitions for the signs in the WHO 2009 Classification.

A consensus on defining these warning signs and severe signs may be built by holding consultative meetings at national and international forums inviting experts from Dengue endemic areas using the Delphi technique. These meetings may be held under the umbrella of WHO where different defining criteria can be evaluated and validated in the light of evidence based data gathered from large multicenter trials .This effort will help standardization of management protocols in dengue patients.

This systematic review raises the question as to what are the essential lab and clinical parameters that must be present and at what time-point in the disease phases, to clearly define or rule out the warning and severe signs in dengue infection. Althought the 2009 WHO classification provides useful guidance on which patients may progress to severe disease using the current WS, a more precise description of these parameters is now needed to allow correct application of these guidelines.

The economic burden of any additional tests and availability and easy access of these investigations needed for defining severity criteria must be taken into consideration before recommending these as part of management guidelines. Also certain criteria may need to be adapted for the differences in the pathophysiology of dengue in paediatric and adult populations.

Standard definitions for the warning signs and signs of severe dengue allow for more effective communication between clinicians, optimal triaging of patients, and identification of patients who require hospitalization as opposed to those who can be treated as outpatients. This can help in preventing unnecessary hospitalizations, which is particularly of paramount importance in the settings of dengue outbreaks. Moreover, standardization helps in harmonizing the interpretation and comparability of dengue epidemiological studies and clinical trials of vaccines.

Our review highlights the heterogeneity in applying the WHO 2009 classification of dengue infection. Though we shed the light on some of the causes for these variations, further investigation is needed to decide on the best approach to address them. In addition, as this review only targeted papers that specifically set out to define the WHO warning signs, it may have missed other studies, where definition of WS was not the main focus. Another limitation is that we restricted our articles to English language as it would be difficult to extract precise definitions from non-English articles due to translation barriers.

Conclusion

There is currently large variation in the application of the WHO 2009 warning sign and severe dengue

classification. More precise definitions are required to create a more standardized approach to this classification system. Future direction should focus on achieving a consensus guideline that is clear and comprehensive but also acceptable, and applicable to clincians and researchers in dengue endemic areas.

Conflict of interest

The authors declare that there is no conflict of interest.

Author contributions

NTH, MEM, KND contributed to study design and analysis. All authors worked on data collection, wrote and approved the manuscript.

Acknowledgments/Funding

We thank “Bridget Wills” (*Centre for Tropical Medicine and Global Health, Nuffield Department of Clinical Medicine, Oxford University, Oxford, UK*) for her contribution in manuscript amendment. This work was supported in part by a "Grant-in-Aid for Scientific Research (B)" (16H05844, 2016–2019 for Nguyen Tien Huy) from Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan and by the Japan Initiative for Global Research Network on Infectious Diseases (J-GRID) for Kenji Hirayama. The funders had no role in the study design, data collection and analysis, decision to publish or preparation of the manuscript.

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Table 1: characteristics of included studies

Author, Year	Study design	Country	Year	N of patients	Mean (median) Age
Weg et al. 2015 (7)	Cohort	Indonesia	2010	157	(20)
Taylor et al. 2015 (8)	Prospective Cohort	Vietnam	2008	143	(23.5)
Hoffmeister et al.2015 (9)	Retrospective case control	Germany	1996 to 2010	56	(35)
Mercado et al. 2015 (10)	Case-control	Philippines	2008	250	9.8
Machado et al. 2014 (11)	Cross sectional	Brazil	2010	288	4.3
Rowe et al. 2014 (12)	Retrospective Study	Singapore	2005	295	ND
Vega et al. 2014 (13)	Cross-sectional study	Colombia	2013	4359	18
Rodrigues et al. 2014 (14)	Retrospective cohort	Brazil	2007	29	56.8
Rathakrishnan et al. 2014 (15)	Cross sectional	Malaysia	2010	504	29.5
Pozo-aguilar et al.2014 (16)	Cross-sectional	Mexico	2009	489	25
Pang, et al. 2014 (17)	Case-control	Singapore	2004 to 2008	135	(44)
Noecker et al. 2014 (18)	Cohort	Indonesia	2011	248	23
Michels et al. 2014 (19)	Cohort	Indonesia	2011 to 2012	77	23
Macedo et al. 2014 (20)	Retrospective cohort	Brazil	2007 to 2008 and 2010 to 2011	450	(8)
Lovera et al. 2014 (21)	Prospective cohort	Paraguay	2011	123	11
Limonta et al. 2014 (22)	Case-control	Brazil	2010	107	40
Carrasco et al. 2014 (23)	Retrospective cohort	Singapore	2006-2008	596	(37)
Yadav et al.2013 (24)	Prospective cohort	India	2010	67	10.4
Weg et al. 2013 (25)	Cohort	Brazil	2010	99	30
Thein et al. 2013 (5)	Retrospective cohort	Singapore	2004, 2007, 2008	1507	34
Prasad et al. 2013 (26)	Cohort	India	2011 to 2012	56	2.9
Natesirinilkul et al. 2013	Cohort	Thailand	2005 to 2010	20	13.6

(27)					
Michels et al. 2013 (28)	Prospective cohort	Indonesia	2012	71	22
Malavige et al. 2013 (29)	Cohort	Sri Lanka	2011	259	26.8
Leo et al. 2013 (30)	Prospective cohort	Singapore	2010-2012	499	34
HanhTien. 2013 (31)	Cohort	Vietnam	2005-2008	1165	10
Guerrero et al. 2013 (32)	Cohort	Colombia	ND	66	69
Gandini et al. 2013 (33)	Cohort	Brazil	ND	43	43
Gan et al. 2013 (33)	Retrospective cohort	Singapore	2004 and 2007	1278	(33)
Aung et al. 2013 (34)	Retrospective cohort	Thailand	2006-2010	323	24
Wieten et al. 2012 (35)	Retrospective cohort	Netherlands	2006 to 2011	581	36
Weg et al. 2012 (36)	Prospective Cohort	Indonesia	2001-2003	173	7
Malavige et al. 2012 (37)	Prospective Cohort	Sri Lanka	2012	112	29.07
Lee et al. 2012 (38)	Retrospective case study	Singapore	2006	690	(35)
Jayaratne et al. 2012 (39)	Prospective cohort	Sri Lanka	2011	184	27.18
Narvaez et al. 2011 (40)	Cross-sectional	Nicaragua	2005-2010	544	(8.5)
Malavige et al. 2011 (41)	Case-control	Sri Lanka		110	30
Low et al. 2011 (42)	Prospective cohort	Singapore	2005-2010	250	(39)
Leo et al. 2011 (43)	Retrospective case control	Singapore	2004-2008	28	(59)
Kalayanarooj et al. 2011 (44)	Prospective	Thailand	2009	274	9.3
Jhambet al. 2010 (45)	Retrospective case control	India	2009	76	28
Basuki et al. 2010 (46)	Prospective cohort	Indonesia	2008	145	ND
Gan et al. 2013(47)	Rereospective cohort	Singapore	2004 and 2007	1278	(32) and (35)
Branco et al. 2014(48)	Case-control	Brazil	2006-2007	95	4.06
Zakaria et al. 2014(49)	Retrospective cohort	Malaysia	2008-2012	281	ND

ND: not detected

Table 2: Reported definitions of warning signs in dengue infection

Author, year	Definition
	Persistent vomiting
Mercado et al. 2014(10)	≥ 6 episodes of vomiting in 24 hours, or Grade 3 and above in the Common Toxicity Criteria Manual
Malavige et al. 2011(41)	≥ 3 episodes of vomiting in 12 hours, and Preventing adequate oral hydration

Carrasco et al. 2014(23) **Gan et al. 2013**(47) **Leo et al. 2011**(43)	Vomiting for ≥2 consecutive days
Aung et al. 2013(34)	Vomiting with signs of dehydration on physical examination
Abdominal pain	
Mercado et al. 2014(10) **Narvaez et al** (40)	Abdominal tenderness or continuous pain or diffuse pain
Vega et al. 2014(13)	Intense and continuous abdominal pain
Macedo et al. 2014(20)	Continuous (not intermittent) abdominal pain
Hoffmeister et al. 2015(9)	Increasing or intense abdominal pain
Lethargy	
Wieten et al. 2012(35)	Alteration of consciousness and/or Glasgow score < 15, or A Blantyre score less than 5
Pozo-aguilar et al. 2014(16) **Macedo et al. 2014**(20)	Alteration of consciousness and/or Glasgow score < 15
Low et al. 2011(42) **Romero-Vega et al. 2014**(13)	Drowsiness and/or irritability

Table 3: Reported definitions of clinical fluid accumulation.

Definition	Number of studies	References
Pleural effusion	17	(5,7–10,14,15,19,20,25,28,40,43,45,46,48,49)
Ascites	17	(5,7–10,14,15,19,20,25,28,40,43,45,46,48,49)
Gall bladder thickening	5	(10,20,28,40,48)
Edema (face & extremities)	1	(8)
Free fluids around urinary bladder	1	(28)
Total	17	

Table 4: Cutoff values used to define "rise in hematocrit".

Refrence	Males	Females	Country
Zakaria et al. 2009 (49)	> 46%	> 40%	Malaysia
Michels et al. 2014 (19)	> 50%	> 44%	Indonesia
Michels et al. 2013 (28)	> 50%	> 44%	Indonesia

Gandini et al. 2013 (33)	> 45%	> 41%	Brazil
Rodrigues et al. 2014 (14)	> 48%	> 48%	Brazil

Table 5: Definition of "rapid decrease in platelet count".

Platelet count	Frequency	Percent	Cumulative %	References
<20,000	2	10.5	9.0	[2, 3]
<50,000	10	52.6	54.5	(12,17,18,20,23,31,33,38,43,47)
<100,000	8	42.1	91.0	(10,13,21,26,39,40,44,45)
<150,000	1	5.3	95.5	(14)
Others*	1	5.3	100.0	(40)
Total	19	100.0		

* Drop in platelet count by 10,000/mm^3 in 24-hours with respect to the previous measurement (**Narvaez et al.**[4]).

Table 6: Definitions of mucosal bleeding in dengue infection.

Definition	Signs and Symptoms	Frequency	Percent (%)	References
Nose bleeding	Epistaxis	15	100	(5,7–10,15,16,23,30,33,34,39,40,45,49)
Gingival bleeding	Gingival bleeding	13	86.7	(7–10,15,16,23,30,33,34,40,45,49)
Gastrointestinal bleeding	Hematemesis, Melena	10	66.7	(7,9,10,15,16,20,39,40,45,49)
Vaginal bleeding	Menorrhagia, metrorrhagia, vaginal bleeding	11	73.3	(8–10,15,20,23,30,33,39,40,49)
Respiratory tract	Hemoptysis	6	40	(10,30,33,40,48,49)
Urinary tract bleeding	Hematuria	5	33.3	(9,10,30,40,49)
Skin bleeding	Petechia, purpura, ecchymoses, bruises	4	26.7	(16,39,48,49)
Eye bleeding	Conjunctival, subconjunctival, retinal	4	26.7	(8,10,15,40)
Ear bleeding		1	6.7	(49)
Total		15	100%	

Table 7: Signs of severe dengue infection.

Definition	Frequency	Percent (%)	References
Shock			
Narrow pulse pressure (<20 mmHg)*	15	88.2	(9,10,12,17,21,23,25,28,29,33,37,39,41,43,47)

Hypotension (< 90 mmHg)	12	70.6	(9,12,17,20,21,23,25,36,42,43,47)
Tachycardia (pulse > 100/min) **	11	64.7	(9,12,17,21,23,25,33,36,42,43,47)
Signs of poor capillary perfusion***	7	41.2	(20,21,24,29,33,39,43)
Total	17	100.00	
Poor capillary perfusion			
Slow capillary refill****	7	100.00	(20,21,24,29,33,39,43)
Cold extremities	7	100.00	(20,21,24,29,33,39,43)
Rapid pulse rate	5	71.43	(20,21,24,29,39)
* Specified by all authors, except for Gandini et al., as pulse pressure <20 mmHg, ** Defined by all authors, except Gandini et al., as pulse rate >100/min *** Signs of poor capillary refill: Slow capillary filling, cold clammy skin, and rapid and weak pulses			
Parameters used to define shock			
1	3	13.04	(10,37,41)
5 and one of 1,2 ,3	1	4.35	(13)
5	2	8.70	(16,48)
1 or 2 or 3	2	8.70	(17,23)
2 and 5	1	4.35	(18)
4 and 1 or 2	1	4.35	(20)
1 and 4	2	8.70	(21,24)
1or 2 or 3 or 5	1	4.35	(9)
1, 2, 3, and 4	1	4.35	(25)
2	1	4.35	(5)
1 and 2	1	4.35	(28)
1 or 4	1	4.35	(29)
1, 2, 3, 4 or 6	1	4.35	(33)
1 or 2 or 3 and 5	1	4.35	(47)
1 or 2	1	4.35	(36)
1 or 4	1	4.35	(38)
1, 2, and 5	1	4.35	(42)
1 or 2 or (3 and 4) or 6	1	4.35	(43)
Total	23	100.00	
1 = Narrow pulse pressure, 2 = Hypotension, 3 = Tachycardia, 4 = Hypoperfusion, 5 = Plasma leakage evident as change in hematocrit >20%, 6 = Undetectable pulse or unrecordable pressure.			
Renal Impairment			
Serum creatinine level × 2 times the upper limit of normal	6	75	(14,17,20,23,43,48)
Serum creatinine level × 2 times the baseline creatinine level	5	62.5	(14,17,20,23,48)
Serum creatinine level> 1.2 mg/dL	1	12.5	(34)
Serum creatinine level> 1.5 mg/dL in	1	12.5	

females and >1.8 mg/dL in males			(9)
Total	8	100	
Severe Bleeding			
GIT bleeding (melena, hematochezia, hematemesis, bleeding per rectum)*	12	92	(9,12,17,18,20,23,27,34,39,43,44,47)
Need for blood transfusion	9	69	(9,12,17,20,23,34,43,44,47)
Vaginal bleeding; menorrhagia or metrorrhagia	7	54	(12,17,18,23,34,43,47)
Severe/ persistent bleeding in the presence of hemodynamic instability	1	8	(20)
Need for acute management to control active bleeding (e.g., nasal packing, dental splint)	1	8	(34)
Total	13	100.00	
* One study, Natesirinilkul et al.[5], specified that GI bleeding should be massive. Another study, Kalayanarooj et al.[6], specified that GI bleeding should be massive and needs blood transfusion.			
Liver Involvement			
AST or ALT > 1000 IU/L	18	94.7	(8,11–14,16–18,20,21,27,34,38–40,43,44,46)
ALF (jaundice, PTT <20%, encephalopathy)	1	5.0	(9)
Total	19	100.00	
Central Nervous System Involvement			
Encephalitis	6	60	(9,18,20,21,32,43)
Encephalopathy*	5	50	(5,9,17,23,43)
Convulsions**	3	30	(9,21,27)
Coma	1	10	(9)
Total	10	100.00	
* Specified as “hepatic encephalopathy” by one study [5] ** Specified as seizures from “posterior reversible encephalopathy syndrome” by one study [5].			
Heart Involvement			
Myocarditis	8	66.67	(17,18,21,23,24,32,43,46)
Heart failure	2	16.67	(40,49)
Myocarditis and heart failure (confirmed by echocardiography)	1	8.33	(20)
Cardiomyopathy	1	8.33	(9)
Total	12	100.00	

Detailed Definitions

Lovera et al. 2014[7]: Myocarditis (elevation of biomarkers: Troponin I or CK-MB) and compatible changes in the electrocardiogram (such as sinus tachycardia with nonspecific ST-segment and T-wave abnormalities). Guerrero et al. 2013[8]: "Myocarditis defined as poor response to therapy with intravenous fluids; alteration in cardiac rhythm (bradycardia or tachycardia) and/or the need for inotropic support added at least one of the following test findings: abnormal thorax X-ray, electrocardiogram alteration (tachyarrhythmia and disorders of ST segment or T wave), pathological echocardiography (systolic or diastolic dysfunction) and biochemical elevation of CKMB isoform."

Table 8: Definitions of respiratory distress.

Author, Year	Definition	Median (range) Age
Aung et al. 2013 (34)	▪ Respiratory rate > 60 breaths/minute ▪ Respiratory discomfort, dyspnea, respiratory failure	≥15
Macedo et al. 2014 (20)	▪ Respiratory rate > 60 breaths/minute ▪ Respiratory discomfory, dyspnea, respiratory failure	(0 – 18)
Weg et al. 2012 (36)	▪ Respiratory rate > 40 breaths/minute ▪ Signs of respiratory distress (dyspnea and tachypnea) ▪ Signs of respiratory acidosis ▪ (PaO2:FiO2) < 200 mmHg	(2 - 14)
Leo et al. 2011 (43)	▪ Respiratory rate > 30 breaths/minute ▪ Oxygen saturation ≤92% on room air, or ▪ Mechanical ventilation	59 (21 – 86)