APPLICATION OF REVISED DENGUE CLASSIFICATION CRITERIA AS A SEVERITY MARKER OF DENGUE VIRAL INFECTION IN INDONESIA

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Abstract. A prospective study of dengue infected patients at Dr.Soetomo Hospital pediatric ward was carried out from October 2008 to April 2009 to evaluate the revised dengue classification system proposed by the Dengue Control (DENCO), for early detection of severe dengue infected patients using the WHO classification system for comparison, with the addition of clinical interventions as a tool to grade for severity. One hundred forty-five patients were included in the study. Using the WHO classification system, 122 cases (84.1%) were classified as having non-severe dengue, of which 70 (48.3%) were classified as having dengue fever (DF), 39 (26.9%) as having dengue hemorrhagic fever (DHF) grade I, and 13 (9%) as having DHF grade II. Twenty-three (15.9%) were classified as having severe dengue, of which 16 (11%) were classified as having DHF grade III and 7 (4.8%) as having DHF grade IV. With clinical interventions included, 8 cases (6.6%) originally classified as having non-severe dengue infection were reclassified as having severe infection (sensitivity=74%, specificity=100%, likelihood ratio (-) =0.26). Using the new dengue classification system, 117 cases (80.7%) were classified as having non-severe dengue infection, of which 79 (54.5%) were classified as having dengue without warning signs and 38 (26.2%) were classified as having dengue with warning signs, while 28 (19.3%) were classified as having severe dengue infection. Using clinical intervention, 4 cases (3.4%) which were originally classified as having non-severe dengue infection were reclassified as having severe dengue infection (sensitivity=88%, specificity=99%, likelihood ratio (+)=98.88, likelihood ratio (-)=0.13). Binary logistic regression showed the revised dengue classification system (p=0.000, Wald:22.446) was better in detecting severe dengue infections than the WHO classification system (p=0.175, Wald:6.339).

Key words: dengue, WHO classification, revised classification, severe dengue, DENCO

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INTRODUCTION

Dengue infection in Indonesia has increased from 0.05 incidents per 100,000 population in 1968 to 35.19 per 100,000 population in 1998. In 2004 the incidence of dengue infection was so high, the government declared the situation as an

outbreak of dengue infection (Sumarmo, 1999).

Dengue fever (DF) and dengue hemorrhagic fever (DHF) occur because dengue virus (DENV) invades the human body through mosquito bites. Dengue viruses, genus *Flavivirus*, family Flaviridae, are comprised of 4 serotypes (DENV 1 - DENV 4). People who have been infected with one serotype of dengue virus, in general, have protection against that same serotype. Protection against a different serotype only lasts a short time after infection. A second infection with a different serotype can lead to dengue hemorrhagic fever. Antibody dependent enhancement (ADE) of infection is one of the most important mechanisms in the pathogenesis of dengue virus infection. These antibodies are formed after primary infection and are assumed to increase the severity of disease. They can also form neutralizing antibodies that provide protection in cases of dengue virus infection (Halstead, 1992; Kurane and Innis, 2002).

Dengue infection presents as a clinical spectrum: asymptomatic, undifferentiated fever, DF and DHF. Classic DF symptoms include fever, headache, muscle pain, retroorbital pain and rash. The main characteristics of the dengue classification system include bleeding, plasma leakage, thrombocytopenia (platelet count $\leq 100{,}000/mm^3$), the presence of hypotension or narrow pulse pressure and clinical signs of shock, leading to the diagnosis of dengue shock syndrome (DSS) (WHO, 1997). The current dengue classification system is useful to identify cases of severe dengue infection for treatment and epidemiological surveillance. However, there can be varying clinical manifestations of dengue infection that do not fit the definitions of the World Health Organization (WHO). Several recent publications have recommended revision of the classifications of severe dengue. One revised dengue classification system from DENCO (Dengue Control) has been studied in several countries in Asia and Latin America with good results (Torres, 2008).

The purpose of this study was to compare the newly revised dengue classification system, which is divided into several levels of severity (dengue with/without warning signs and severe dengue), with the WHO classification system (DF/DHF/DSS) for the identification of severe cases with/without unusual manifestations.

MATERIALS AND METHODS

Patients and clinical procedures

A prospective analytic observational study was conducted from October 2008 to July 2009 among dengue virus infected pediatric patients at Dr.Soetomo Hospital, Surabaya, Indonesia. Patients aged 0-13 years with suspected dengue virus infection based on WHO diagnostic criteria were included consecutively in the study. Exclusion criteria were patients with hematologic disorders and severe heart or lung diseases. Patients who did not meet WHO diagnostic criteria but were clinically suspected to have dengue virus infection were included in the study. The research team recorded the data on a standard data collection sheet. The subjects were classified at the time of admission using both the standard WHO classification system and the new dengue classification system proposed by the Dengue Control (DENCO) study. A standard physical examination and complete blood count were done daily. Blood chemistry and X-ray images were taken to monitor the course of the disease, especially during the defervescence period. Guidelines for clinical interventions in patients were

according to WHO guidelines. This was also used as a standard tool for grading the disease severity of each patient.

Diagnostic procedures

Blood sampling was performed for serological tests (IgG and IgM anti-dengue), PCR and culture and isolation of the virus. These examinations were performed on admission and at the time of fever defervescence to confirm the diagnosis of dengue virus infection. Patients with one or more positive diagnostic tests were confirmed as having dengue virus infection, whereas those with negative results were excluded.

Statistical analysis

The data were analyzed to determine the ability of the classification systems to adequately classify the patient compared to the clinical course. Analyses were performed using SPSS 16.0,0, using the Mann-Whitney test, then binary logistic regression was used to compare the two classification systems. A *p*-value ≤0.05 was considered statistically significant.

RESULTS

One hundred forty-five patients were studied, they consisted of 68 boys and 77 girls (Fig 1). The signs and symptoms of the patients at the time of admission varied, as can be seen in Table 1. Using the WHO classification system, 122 cases (84.1%) were classified as having nonsevere dengue infection, which were comprised of 70 patients (48.3%) with dengue fever (DF), 39 (26.9%) with dengue hemorrhagic fever (DHF) grade I and 13 (9%) with DHF grade II. Twenty-three cases (15.9%) were classified as having severe dengue infection, which were comprised of 16 patients (11%) with DHF grade III and 7 (4.8%) with DHF grade IV. Using

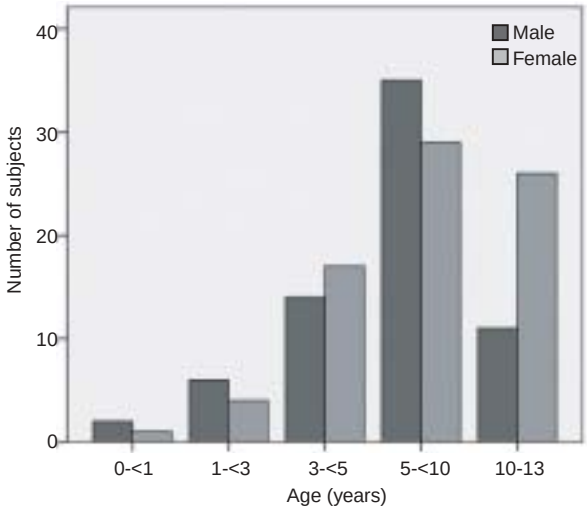

Fig 1–Dengue infection subjects by age and sex.

clinical intervention, 8 cases (6.6%) classified as being nonsevere dengue infection using WHO criteria were reclassified as severe (sensitivity=74%, specificity=100%, likelihood ratio (-)=0.26). Using the new dengue classification system, 117 cases (80.7%) were classified as having non-severe dengue infection, which were comprised of 79 cases (54.5%) of dengue infection without warning signs and 38 cases (26.2%) of dengue infection with warning signs. Twenty-eight cases (19.3%) were classified as having severe dengue infection. Using clinical intervention, 4 cases (3.4%) classified as having non-severe dengue infection were reclassified as having severe dengue infection (sensitivity=88%, specificity=99%, likelihood ratio (+)=98.88, likelihood ratio (-)=0.13).

These two classification systems were compared concerning the ability of detecting severe dengue infection cases, with clinical intervention as a tool for grading the severity of the disease (Table 2). Clinical intervention was influenced by bleeding score and level of clinical care (Fig 2)

Table 1
Symptoms and signs in subjects with dengue infection.

Clinical	*N* (percent)
Aches or pain	74 (51.0)
Petechial rash	20 (13.8)
Decrease in appetite	34 (23.4)
Abdominal tenderness	32 (22.1)
Persistent abdominal pain	6 (4.1)
Persistent vomiting	7 (4.8)
Palpable liver >2 cm below costal margin	38 (26.2)
Fluid accumulation[a]	31 (21.4)
Fluid accumulation[a] with respiratory distress	9 (6.2)
Lethargy / anxiety	26 (17.9)
Shock	31 (21.4)
Tourniquet test positive	103 (71)
Mucosal bleeding	25 (17.2)
Decreased consciousness	4 (2.8)
Severe organ involvement[b]	5 (3.4)

[a]any interstitial fluid accumulation (pleural effusion, ascites) proven by clinical and/or radiological examination.
[b]one patient had severe liver impairment (ALT >1,000 U/l).

for each subject. Using the Mann-Whitney test it appears both the WHO classification system (p=0.000, Z=7.385) and the new dengue classification system (p=0.000, Z=8.993) were equally good. When these two classification systems were compared using binary logistic regression, the new dengue classification system (p=0.000, Wald:22.446) was better in detecting severe dengue virus infection cases compared with the WHO classification system (p=0.175, Wald:6.339).

DISCUSSION

From the results of this study, the newly revised dengue classification system appears to be better at detecting severe dengue infection than the WHO classification system. The new revised dengue classification system had a higher sensitivity and good specificity.

Previously studied by Balmaseda *et al* (2005), Bandyopadhyay *et al* (2006), and Setiati *et al* (2007), all stressed the need for a new revised classification system for dengue virus infection. This was based on the fact that severe dengue infection cases seen in significant numbers did not fully fit the WHO classification system, and were grouped as unusual manifestations. The newly revised classification system would be an alternative to overcome these shortcomings. For this reason, the TDR/WHO (Program of Training and Research on Transmissible Diseases of the World Health Organization) sponsored an international study called DENCO (Dengue Control) with the main objective of obtaining information from a large number of patients with confirmed dengue; they found a better classification system, also identifying the warning signs that would be useful to improve dengue case management protocols. Clinical information was obtained from nearly 2,000 patients with confirmed dengue, conducted in 7 countries from 2 continents. This study concluded that 18-40% of cases could not be classified by the current WHO classification system, and > 15% of cases with shock could not be classified as severe cases of dengue, since they did not meet some of the criteria of DHF/DSS (Torres, 2008).

The criteria of severe dengue infection include severe plasma leakage, expressed in hypovolemic shock, and/or breathing difficulty due to excess accumulation of fluid in the lungs, severe bleeding according to the criteria used by doctors, and organ involvements, including severe hepatitis due to dengue (transaminase >1,000 units), encephalitis due to dengue,

Bleeding score:

0. No bleeding.
1. Skin bleeding that is not clinically significant **or** positive. Tourniquet test **or** urine test spurious.
2. Any other bleeding that is not clinically significant.
3. Any severe bleeding.

Clinical care level:

1. In- and outpatients, able to walk aroud, standard observation protocol.
2. Hospitalized patients, where clinicians demand close observation protocol.
3. Hospitalized patients, where clinicians demand ICU level care.

Source: Wills and Jänisch, 2007

Fig 2–Bleeding score and the level of clinical care used for determining the criteria for clinical interventions.

Table 2
Intervention criteria to determine the degree of clinical disease.

	Category (reference)	Category (moderate)	Category (severe)
Plasma leakage	• No IV fluids • Clinical care level 1 only	• IV fluids: crystalloids for maintenance only • IV crystalloids for rehydration and care level 1 or 2	• Shock resuscitation • IV colloids • IV crystalloids for rehydration and care level 3 • Oxygen therapy or assisted ventilation
Bleeding	• Bleeding score 0,1 and 2 as long as clinical care level 1	• Bleeding score 2 and no blood products or only platelets • Bleeding score 3 and no blood products	• Blood products other than platelets given • Platelets and bleeding score 3
Organ impairment		• Diuretics and no other intervention	• Inotropic drugs • Spec. treatment liver failure • Dialysis/treatment renal failure • Treatment CNS impairment

Source: Wills and Jänisch, 2007

or serious damage to other organs, such as dengue myocarditis (Fig 3). This severity criteria has 95% sensitivity and 97% specificity (Torres, 2008).

DENCO criteria can also identify some signs and symptoms that occur in patients 1 day before deterioration of conditions. These warning signs allow early identification of high risk dengue patients allowing doctors a chance to begin early treatment by replacing fluids intravenously and improving the patient's prog-

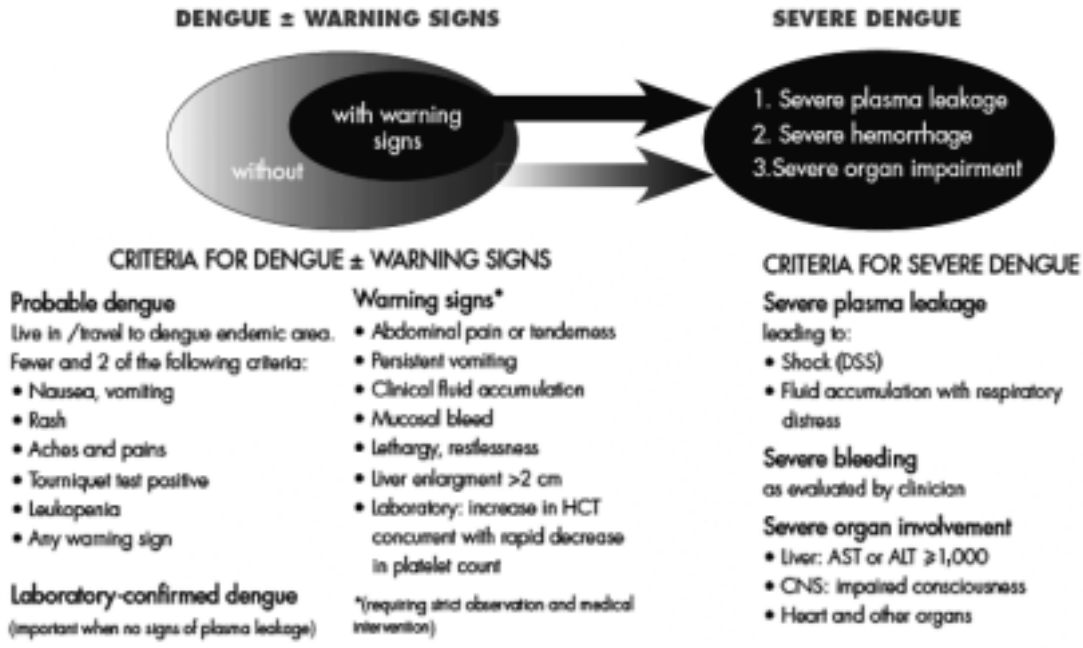

Fig 3–Revised dengue classification (WHO, 2009).

nosis. Abdominal pain or tenderness on abdominal examination are significant risk factors in adults and children, as well as mucosal bleeding, and thrombocytopenia less than 10,000/mm^3. In adults, other danger signs include lethargy, irritability, hypoalbuminemia, and an elevated hematocrit (Torres, 2008).

In this study clinical interventions were used as a tool for grading the severity of the disease (Table 2 and Fig 3). There are 3 levels of severity according to clinical intervention criteria: mild, moderate and severe. There are 3 patient groups based on these criteria: group A (patient may be sent home/outpatient treatment), group B (patient must be hospitalized for close observation and medical treatment), and group C (requiring intensive emergency treatment) (Torres, 2008). In this study there were only 2 intervention groups: moderate (group B, 114 patients) and severe (group C, 31 patients) could be defined. By applying WHO criteria, there were 8 patients with a diagnosis of DF and DHF grade II who later developed shock (DSS, severe dengue). Using the revised dengue classification criteria 4 cases belonging to the dengue group with warning signs were later moved into the severe dengue group. This indicates the revised dengue classification system may be better at predicting the occurrence of severe dengue infection.

One patient had severe liver involvement (ALT > 1,000 U/l) which, according to the revised dengue criteria, should be classified as severe dengue infection, although only moderate clinical interventions were required. This fact shows comprehensive patient assessment is required to predict the severity of the disease.

This study had some limitations, such as the limited number of samples, which also limited the comparative analysis between these two classification systems. In this study, the WHO standards guidelines of 1997 were used for management

of dengue infected patients, leading to differences in patient triage methods and management when compared with the DENCO revised clinical management guidelines.

In summary, this study shows the revised dengue classification system may be better at detecting severe dengue infection cases compared to the WHO classification system. Further research is needed with larger numbers of cases in multiple centers, using of the revised clinical management guidelines.

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